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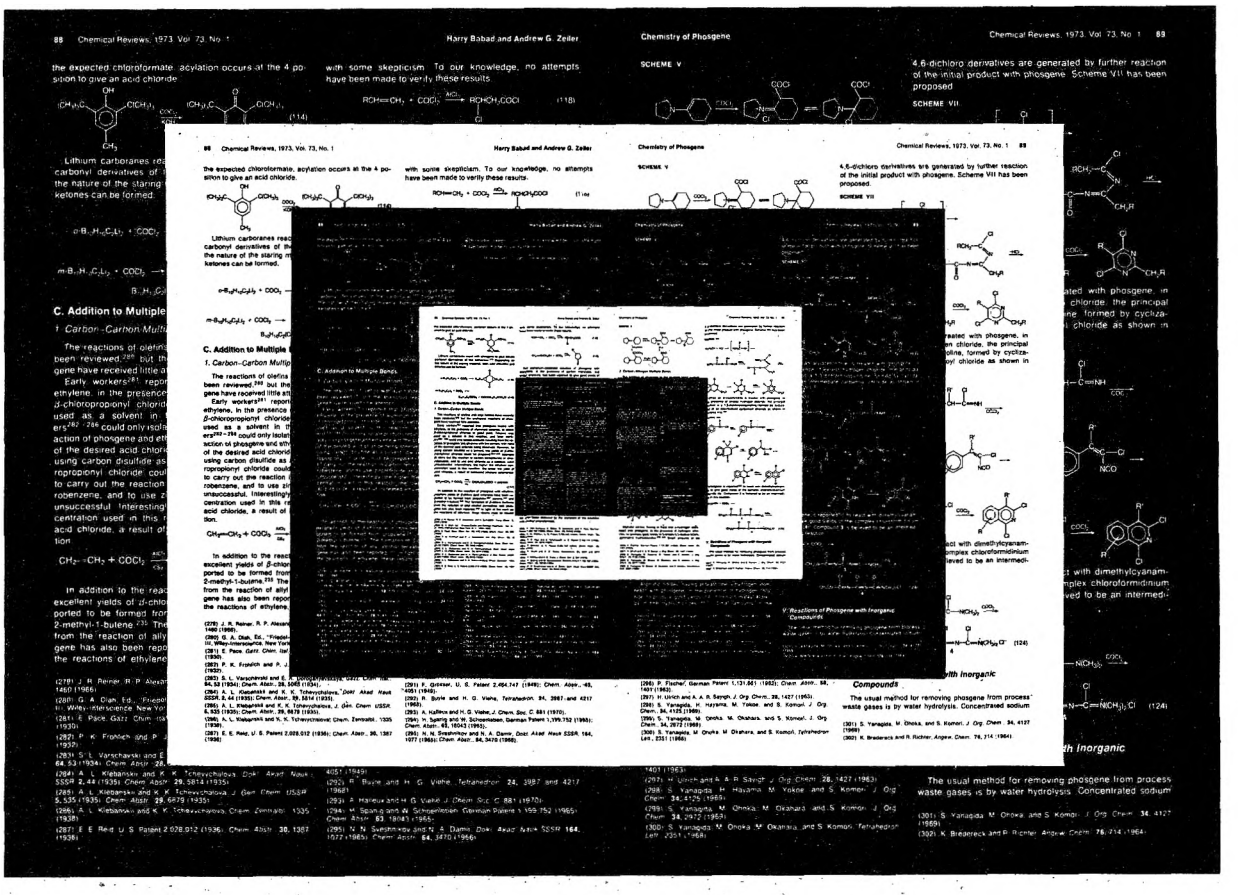

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JUNE 1, 1973

The Chemistry of the Base-Catalyzed Condensation of Some 3-Alkoxy- and 3-Alkoxy-2-dialkoxymethyl Esters with Ureas. Synthesis of 5-Substituted Uracils[1]

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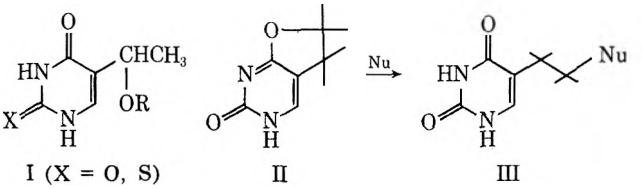
Received January 8, 1973

The formylation reaction of methyl 3-methoxybutyrate and the scope and limitations of the condensation of methyl 2-dimethoxymethyl-3-methoxybutyrate with ureas were studied. The former reaction is a complex one yielding numerous products, a number of which [*i.e.*, dimethyl (2-ethylidene-3-methyl)glutarate, methyl 2-dimethoxymethyl-3-methoxybutyrate, and dimethyl 4-methylisophthalate] were isolated. Under conditions favoring formation or accumulation of ionic intermediates, the yields of the glutarate and isophthalate derivatives increases while that of the 2-dimethoxymethyl-3-methoxybutyrate decreases. A mechanism is proposed explaining the formation of these products. The condensation of 2-dimethoxymethyl-3-methoxybutyrate with urea or dinitrophenylhydrazine in acid yields, respectively, 5-carbomethoxy-4-methyl-3,4-dihydropyrimidin-2-one and a pyrazoline. Base-catalyzed condensation of the same material with ureas produces 5-substituted uracils such as 5-(1-methoxyethyl)-2-thiouracil, 5-(1-thiocarbamylaminoethyl)-2-thiouracil, 5-vinyl-2-thiouracil, 5-vinyluracil, and 5,6-dihydro-5-dimethoxymethyl-6-methyl-2-thiouracil. Factors affecting the course of this reaction were explored and a comprehensive mechanism is proposed in which a series of interconvertible intermediates lead to the several pyrimidines obtained. The synthesis of 5,6-dihydro-6-methyl-2-thiouracil from methyl crotonate or methyl 3-methoxybutyrate and thiourea, and studies on the chemical reactivity of that reduced pyrimidine, are reported.

In a previous report we described the synthesis of 5-vinyluracil by the decarboxylation of 3-(5-uracilyl)-propenoic acid.[2] Because of the low yield obtained in that synthesis, and the need for larger quantities of the vinyl compound to study its chemical and biological activity, we explored alternative preparative routes. One procedure that appeared to be of greater synthetic value in the pyrimidine field was the base-catalyzed condensation of urea derivatives with esters of 3-alkoxycarboxylic acids such as $CH_3CH(OCH_3)C(H)(X)COOR$ where X represents a vinyl ether (=CHOR) or an acetal [$-CH(OR)_2$] function. Appropriate derivatives of the resulting 5-(1-hydroxyethyl)uracil (I, Scheme I) should be more readily converted *via* an

SCHEME I



elimination reaction to the 5-vinyl compound, in contrast to those of the 2′ isomer which, through the furan derivative II, preferentially give substitution products (III).[2] However, I, being a vinylogous carbinolamine which also possesses a C-1′ allylic carbon atom, could, in addition, be reactive toward nucleophiles in the presence of either an acidic or a basic catalyst. Numerous examples of substitution reactions involving uracil derivatives structurally related to I have been reported[3-7] and mechanistically rationalized.[8-11] Those mechanistic interpretations have been considered in relation to the results reported here.

A. Formylation of Methyl 3-Methoxybutyrate.—Conversion of methyl crotonate (1) to methyl 3-methoxybutyrate (3) was accomplished by the general method of Rehberg and Fisher,[12] with the crude product usually obtained in over 70% yield. The subsequent formylation of **3** (Scheme II) proved to be complex, with numerous products resulting, and its mechanistic aspects deserve consideration. Several prod-

(1) This investigation was supported in part by funds from the National Cancer Institute (Grant No. CA 08748) and the American Cancer Society (Grant No. P 295).

(2) J. D. Fissekis and F. Sweet, *J. Org. Chem.*, **38**, 264 (1973).

(3) J. A. Carbon, *ibid.*, **25**, 1731 (1960).

(4) A. Giner-Sorolla and L. Medrek, *J. Med. Chem.*, **9**, 97 (1966).

(5) Z. A. Martiroyan, V. I. Gundar, and S. I. Zav'yalov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1841 (1970); *Chem. Abstr.*, **74**, 54134 (1971).

(6) H. Guglielmi and B. Athen, *Hoppe-Seyler's Z. Physiol. Chem.*, **350**, 809 (1969).

(7) R. Brossmer, *Angew. Chem., Int. Ed. Engl.*, 702 (1967).

(8) R. W. Chambers, *Progr. Nucl. Acid Res. Mol. Biol.*, **5**, 349 (1966).

(9) D. V. Santi, *J. Heterocycl. Chem.*, **4**, 475 (1967).

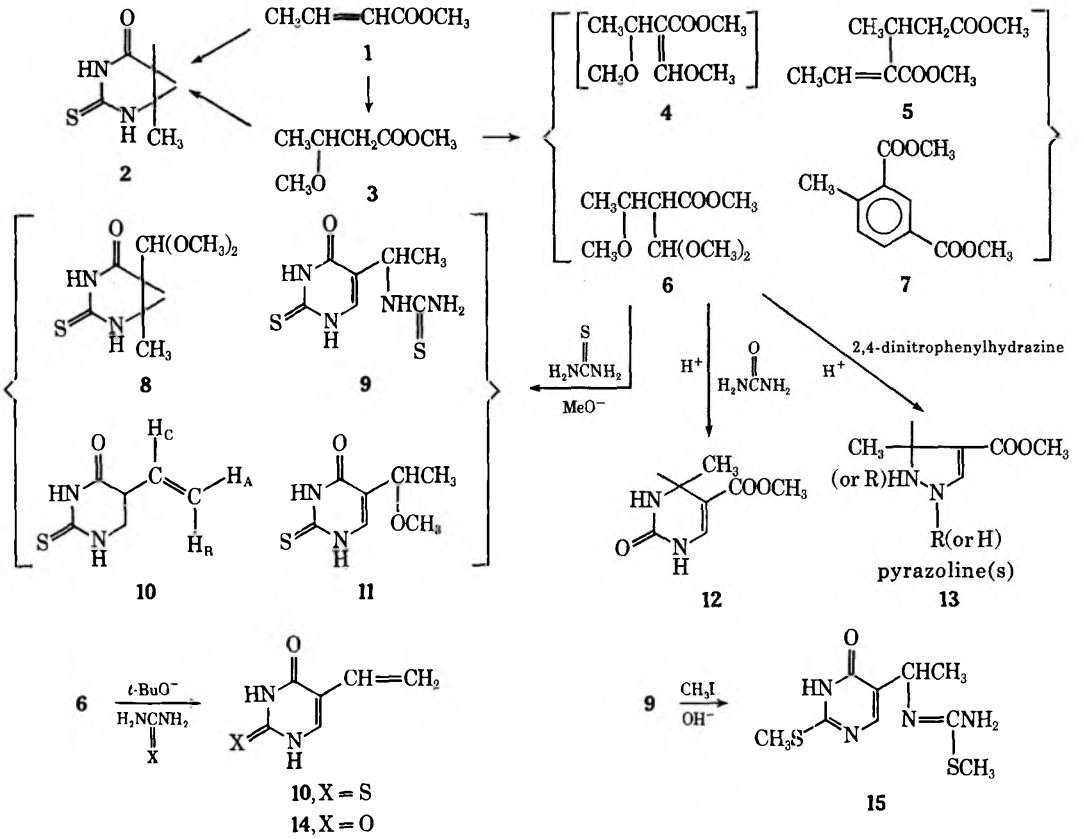
(10) D. V. Santi and A. L. Pogolotti, Jr., *ibid.*, **8**, 265 (1971).

(11) U. Lerch, M. G. Burdon, and J. G. Moffatt, *J. Org. Chem.*, **36**, 1507 (1971).

(12) C. E. Rehberg and C. H. Fisher, U. S. Patent 2,504,151 (April 18, 1950).

ucts of this reaction were isolated and characterized, *i.e.*, dimethyl (2-ethylidene-3-methyl)glutarate (**5**), methyl 2-dimethoxymethyl-3-methoxybutyrate (**6**), and dimethyl 4-methylisophthalate (**7**); some others, apparently polymeric, were not identified. A modification of the procedure used for the formylation of 3-alkoxypropionates[13-15] was applied to the reaction of methyl 3-methoxybutyrate (**3**) with methyl formate in the presence of CH_3ONa. The intermediate resonance-stabilized ambident anion $[CH_3CH(OCH_3)C(CHO)COOCH_3]^-$ was then alkylated with dimethyl sulfate. By analogy to the products obtained from the 3-alkoxypropionates,[13-15] the methyl 2-methoxymethylene-3-methoxybutyrate (**4**), which is the initial product expected, is then converted to the corresponding acetal, methyl 2-dimethoxymethyl-3-methoxybutyrate (**6**), which was isolated. Since the alkylation of the ambident anion is a highly heterogeneous reaction, no meaningful conclusions can be drawn regarding factors affecting the oxygen *vs.* carbon alkylation ratio.[16] The base-catalyzed addition of alcohols to enol ethers is well known[17-19] and formation of **6** undoubtedly occurs by addition of excess CH_3O^- to the vinyl ether **4**.

SCHEME II



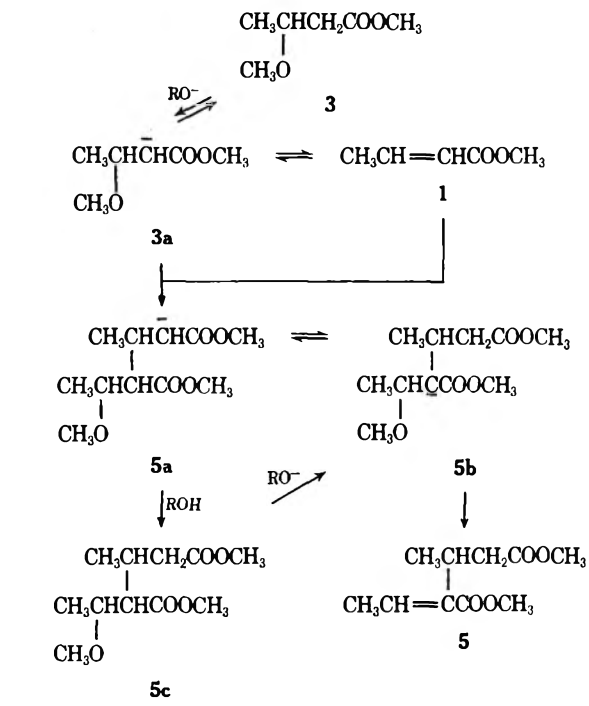
The formation of the dimeric dimethyl (2-ethylidene-3-methyl)glutarate (**5**), which arose during the formylation of **3**, is reasonably interpreted by a Michael-type addition as shown in Scheme III. The species **3a**[20] can react competitively, either with the formate[21] leading eventually to **4** (Scheme II), or with **1** formed *in situ*,[22,23] to give **5** by either of two routes.

Dimethyl 4-methylisophthalate (**7**) was also isolated from the formylation mixture and identified by comparison (melting point, mixture melting point, ir, and pmr spectra) with an authentic sample prepared (Scheme IV) by the oxidation of 2,5-dimethylbenzoic acid with potassium permanganate,[24] followed by esterification of the resulting 4-methylisophthalic acid (**17**).

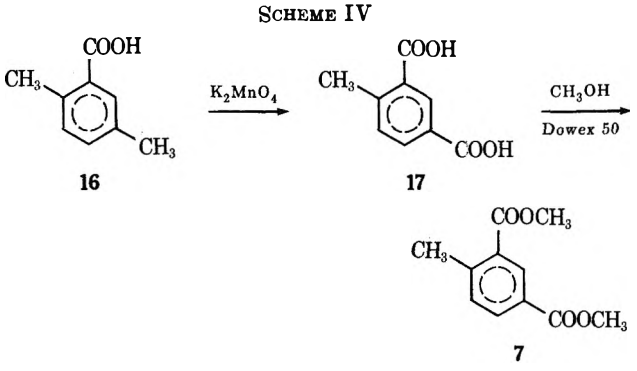
A mechanism (Scheme V) for the formation of **7** involves the reaction, *via* a Michael condensation, of two of the obligatory intermediates from the overall formylation reaction **3a** and **4**[26] to form **7a**, which then gives

(13) A. Takamizawa, *Yakugaku Zasshi*, **74**, 752 (1954).
(14) A. Takamizawa, K. Tokuyama, and H. Satch, *ibid.*, **79**, 664 (1959).
(15) A. Takamizawa, K. Hirai, and S. Sumimoto, *Chem. Pharm. Bull.*, **14**, 238 (1966).
(16) W. J. LeNobel and H. F. Morris, *J. Org. Chem.*, **34**, 1969 (1969).
(17) E. Schmitz and I. Eichhorn, "The Chemistry of the Ether Linkage," S. Patai, Ed., Interscience, New York, N. Y., 1967, p 323.
(18) M. F. Shostakovskii, A. V. Bogdanova, and G. I. Plotnikova, *Russ. Chem. Rev.*, **33**, 66 (1964).
(19) E. Takamizawa, Japanese Patent 10,776 (1956); *Chem. Abstr.*, **52**, 15585 (1958).
(20) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N. Y., 1968, p 568.
(21) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 735.
(22) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, p 1019.
(23) The ElcB mechanism of the retrograde process has been confirmed: S. Patai, S. Weinstein, and Z. Rappoport, *J. Chem. Soc.*, 1741 (1962).
(24) W. H. Bentley and W. H. Perkin, Jr., *J. Chem. Soc.*, **71**, 157 (1897). The oxidation produced only **17** and none of the isomeric 4-methylphthalic acid. This was established by chromatography on a Sephadex G-10 column and comparison of its pmr spectrum to that of 4-methylphthalic acid.[25]
(25) Purchased from Eastman Kodak.
(26) The inclusion of species **3a** is supported by the fact that unreaeted starting material, *i.e.*, **3**, has always been found in the final crude mixture containing **6**.

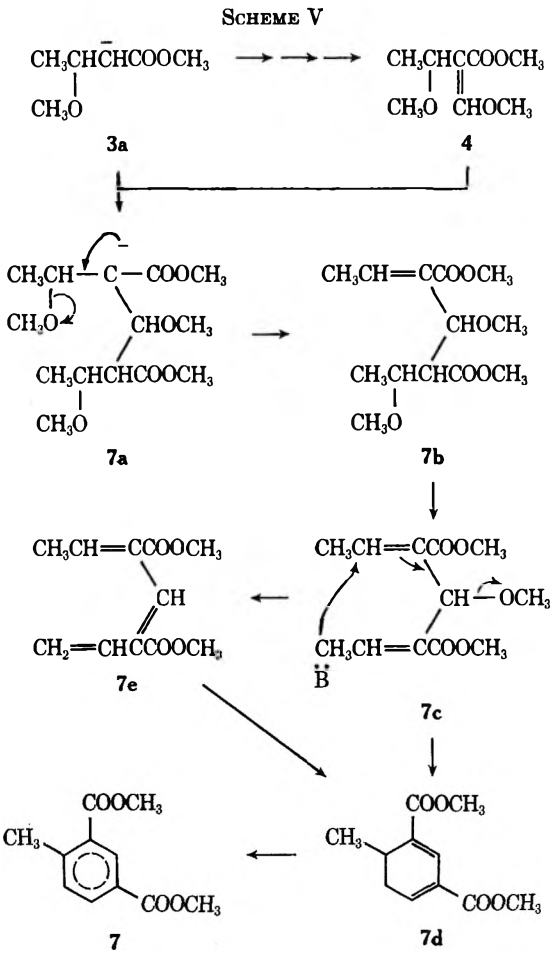
Scheme III



Scheme IV



Scheme V



7c. Cyclization[27] to the cyclohexadiene derivative **7d** is presumed to be followed by air oxidation to dimethyl 4-methylisophthalate (**7**), an aromatization known to occur with atmospheric oxygen.[31]

With the intermediates **3a** and **4** common to the reactions in Schemes II, III, and V, and with similar addition–elimination steps involved, the mechanisms proposed in those schemes are consistent and mutually support each other. Under conditions which promote the formation or accumulation of the ionic species **3a**, the secondary products, **5** and **7**, predominate in the reaction mixture. With a small volume of benzene as solvent and slowly reacting slices of sodium, a satisfactory yield, up to 36%, of the acetal **6** was obtained. On the other hand, when the more polar solvent ethyl ether and/or the faster reacting sodium hydride were used, the yield of **6** was decreased, or became nil, while that of the products **5** and **7** increased. This control of the course of the reaction supports the ionic mechanisms proposed in Schemes III and V.

B. Cyclizations of Methyl 2-Dimethoxymethyl-3-methoxybutyrate to Pyrimidines.—The acid-catalyzed condensation of **6** with urea gives the 5-carbomethoxy-4-methyl-1,2,3,4-dihydropyrimidin-2-one (**12**).[32] Analytical and pmr data were consistent with structure **12** and it possessed the characteristic uv absorption properties of the 5-carbomethoxy-1,2,3,4-dihydropyrimidin-2-ones.[33] In an analogous manner the reaction of **6** with 2,4-dinitrophenylhydrazine in acid led to the pyrazoline derivative(s) **13**. Tlc data suggest the presence of only one isomer. However, because of poor solubility, pmr measurements were not conclusive as to the position of attachment (N^1 *vs.* N^2) of the dinitrophenyl group.

Base-catalyzed condensation of **6** with ureas yielded products of much greater interest. To our knowledge syntheses of pyrimidines by base-catalyzed condensation of such compounds with weak nucleophiles such as urea and thiourea were previously unknown. Although pyrimidines are commonly obtained by condensations of acetals of 1-aldehydo-2-alkoxy esters or nitriles with

(27) The cyclization to **7d** could be a concerted reaction involving the abstraction of an allylic proton from one of the terminal methyl groups, followed by an intramolecular attack of the incipient carbanion to the opposite chain with displacement of methoxide ion. Alternatively, the abstraction of an allylic proton leads to a conjugated triene **7e**, which then cyclizes to **7d**. Thermally induced ring closure of conjugated trienes, having a central cis double bond to give cyclohexadienes, is a well-established reaction, but it requires, in general, rather vigorous conditions (*e.g.*, heating at 130–200°).[28,29] Mechanistically, taking into consideration the electronic structure of the open-chain triene **7e**, such an electrocyclic transformation to **7d**, seems feasible.[30]

(28) E. N. Marrell, G. Caple, and B. Schatz, *Tetrahedron Lett.*, 385 (1965).

(29) E. Havinga and J. L. M. A. Schlatmann, *Tetrahedron*, **16**, 146 (1961).

(30) R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **87**, 395 (1965).

(31) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N. Y., 1968, p 861.

(32) The formation of **12** is in harmony with the results obtained from the acid-catalyzed condensation of 2-alkoxymethylene-3-alkoxypropionates with ureas: (a) A. Takamizawa and K. Hirai, *Chem. Pharm. Bull.*, **12**, 1418 (1964); (b) A. Takamizawa and K. Hirai, *ibid.*, **12**, 804 (1964).

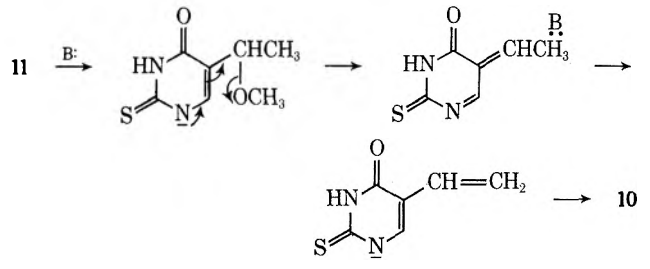
(33) F. Sweet, unpublished results.

amidines,[34-38] the only examples with a urea involve the more nucleophilic *N*-benzyloxyurea.[39]

From the reaction of the acetal **6** and thiourea in sodium methoxide–methanol, the following four products were isolated and characterized: 5-(1-methoxyethyl)-2-thiouracil (**11**), 5-(1-thiocarbamylaminoethyl)-2-thiouracil (**9**), 5-vinyl-2-thiouracil (**10**), and 5-dimethoxymethyl-5,6-dihydro-6-methyl-2-thiouracil (**8**). The substituted 5-alkyl-2-thiouracils **11** and **9** are the major ones. It is thus apparent that **6** in basic media reacts either as an aldehyde–ester giving **9**, **10**, and **11** or as an ether–ester leading to **8**. The synthesis of **11** by this reaction is of particular importance. 5-hydroxymethyl-2-thiouracil, of which **11** is the next higher homolog, has been prepared by the condensation of formaldehyde with 2-thiouracil;[40,41] however, attempts to form higher homologs by condensation of pyrimidines with aldehydes have had but limited success.[42]

Mechanistic aspects of the complex reaction of **6** with thiourea were investigated. The possibility that **11** could react in a manner analogous to that described for the O-1′ *p*-nitrophenyl ethers or acetates of 5-hydroxymethyluracils[10] (Scheme VI) was considered.

SCHEME VI



However, it was established that the products **9**, **10**, and **11** are not interconvertible under the experimental conditions used. When **11** was refluxed in methanol–sodium methoxide in the presence or absence of thiourea, it was stable, as shown by chromatography over a Dowex-50 (H^+) column and by tlc. Similar negative results were obtained under more vigorous conditions with *tert*-butyl alcohol and sodium *tert*-butoxide at reflux or heated at 140°. The 5-vinyl compound **10** is less stable in the methanol–sodium methoxide solvent but still no **9** or **11** could be derived from it. The acetal **6** must therefore be undergoing specific changes, before the several final cyclizations. Despite considerable studies, the mechanism of condensation of 2-dialkoxymethyl-3-alkoxypropionitriles or esters to give pyrimidines remains controversial.[43] We now propose, and present support for, a more comprehensive mechanism (Scheme VII) in which a series of interconvertible intermediates lead to the several pyrimidines obtained.

From the carbanion **6a** (Scheme VII), elimination of a methoxide ion could proceed in either of two ways to give the vinyl ether **6c** or the crotonamide **6b**. Cyclization of **6c** will produce **11**. A similar intramolecular Michael addition will produce **8** from **6b**. Alternatively, **6b** leads to **9** and **10**.

Several additional experiments provide support for these mechanisms. Methyl crotonate (**1**) or methyl 3-methoxybutyrate (**3**) were treated with thiourea in methanol–sodium methoxide, and the product of these reactions proved to be 5,6-dihydro-6-methyl-2-thiouracil (**2**).[45] As the 5,6-dihydro-2-thiouracils can be readily oxidized to the corresponding 2-thiouracils[47] and thence to uracils, the present method provides a synthetic route for the preparation of 6-substituted uracil derivatives from 2,3-unsaturated or 3-alkoxy esters.

The 5,6-dihydro-6-methyl-2-thiouracil (**2**) is unstable in alkaline solution. This was evidenced by rapid loss of uv absorption at 272 nm which was accompanied by the appearance of a new band at 238 nm. Data suggesting that the new absorption band is due to the species $NH_2C(=S)NHCH(CH_3)CH_2COO^-$ are in the Experimental Section. These results are reminiscent of the reported reactivity of 5,6-dihydro-2-thiouracils toward nucleophiles.[48,49] By analogy it is proposed that in alkaline solutions **2** undergoes the addition of OH^- to give first **2a**, which is then cleaved to **2b** (Scheme VIII). Upon neutralization of the latter **2d** results. This sequence is comparable to the $B_{Ac}2$ mechanism of amide hydrolysis.[50] The uv spectral properties and chemical reactivity of the product obtained are in harmony with those expected for **2d**. Although adducts of the **2a** type (neutral form) have been prepared,[49] that structure is excluded by pmr data, which do support structure **2d**.

The susceptibility of 5,6-dihydro-2-thiouracils to base-catalyzed nucleophilic addition both explains the low yield of **8** and provides further support for portions of the mechanism proposed in Scheme VII. The addition of CH_3O^- to the C-4 carbonyl group of **8** followed

(34) A. Takamizawa, K. Hirai, and T. Ishiba, *Chem. Pharm. Bull.*, **14**, 1450 (1966).

(35) A. Takamizawa, K. Tokuyama, and K. Tori, *Bull. Chem. Soc. Jap.*, **32**, 188 (1959).

(36) A. Takamizawa and K. Hirai, *Chem. Pharm. Bull.*, **12**, 393 (1964).

(37) T. Nishino, Y. Miichi, and K. Tokuyama, *Tetrahedron Lett.*, 4335 (1970).

(38) T. Nishino, M. Kiyokawa, Y. Miichi, and K. Tokuyama, *Bull. Chem. Soc. Jap.*, **45**, 1127 (1972).

(39) (a) W. Klötzer, *Monatsh. Chem.*, **95**, 1729 (1964); (b) *ibid.*, **96**, 169 (1965).

(40) M. Calligaris, S. Fabrissin, M. DeNardo, and C. Nisi, *J. Org. Chem.*, **36**, 602 (1971).

(41) L. Monti and C. Pacini, *Gazz. Chim. Ital.*, **78**, 638 (1948).

(42) T. L. V. Ulbricht, *Progr. Nucl. Acid Res. Mol. Biol.*, **4**, 199 (1965).

(43) For example, Takamizawa[44] favors the initial formation of $C_2H_5OCH_2C(CN)=CHN=C(CH_3)NH_2$ from 1-methoxy-1-ethoxypropionitrile and acetamidine, which then undergoes cyclization to the 5-ethoxymethyl-4-amino-2-methylpyrimidine. On the other hand, Nishino and coworkers[34,35] have proposed different mechanisms, arguing against the involvement of the previously described intermediate because of the known inertness of acetals to solvolysis.

(44) A. Takamizawa, K. Tokuyama, and K. Tori, *Bull. Chem. Soc. Jap.*, **32**, 188 (1959).

(45) This represents a facile one-step method for the preparation of 5,6-dihydro-2-thiouracils previously prepared by cyclization of substituted thioureas: V. Skaric, B. Gaspert, I. Jerkunica, and D. Skaric, *Croat. Chem. Acta*, **37**, 199 (1965). In a similar reaction unsaturated ketones have been condensed directly with thiourea under alkaline conditions, but the products were 3,4,5,6-tetrahydropyrimidines.[46]

(46) (a) E. J. Nikawitz, U. S. Patent 3,152,122 (1964); *Chem. Abstr.*, **62**, 1670 (1965). (b) R. Zimmermann, B. Brähler, and H. Hotze, German Patent 1,065,849 (1959); *Chem. Abstr.*, **55**, 8439 (1961).

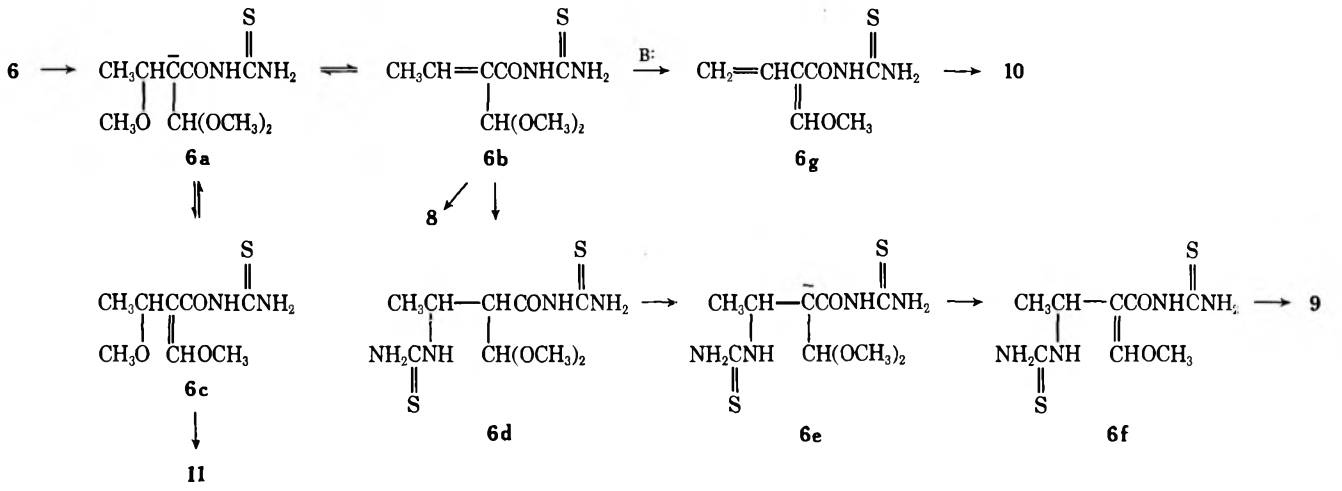
(47) B. R. Baker and J. L. Kelley, *J. Med. Chem.*, **11**, 682 (1968).

(48) V. Skaric and B. Gaspert, *Chem. Commun.*, 550 (1968).

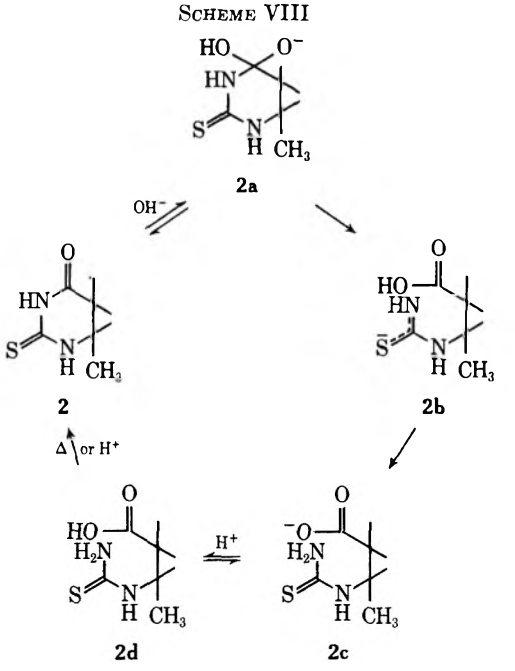
(49) V. Skaric and B. Gaspert, *J. Chem. Soc. C*, 2631 (1969).

(50) (a) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N. Y., 1968, p 314. (b) The work of Sander on the alkaline hydrolysis of the 5,6-dihydrouracils also supports our proposal: E. G. Sander, *J. Amer. Chem. Soc.*, **91**, 3629 (1969).

Scheme VII



Scheme VIII



by opening of the ring and reaction of the resulting ester with a second molecule of thiourea would give intermediate **6d**. Thus **8** could be a precursor of **9**, although we did not investigate this possibility because of the very small quantity of **8** available. An analogous overall conversion of 5,6-dihydro-2-methyl-5-dimethoxymethyl-4-pyrimidinone to 5-acetiminoaminomethyl-2-methyl-4-pyrimidinone has been reported.[37]

C. Factors Influencing the Condensation of 6 with Ureas.—Control of the course of this condensation reaction could be achieved by treating **6** with thiourea or with urea in *tert*-butyl alcohol–sodium *tert*-butoxide. Under these conditions the only major products were 5-vinyl-2-thiouracil (**10**) or 5-vinyluracil (**14**), in yields of ~30%. This is a much more practical yield for 5-vinyluracil than that obtained *via* 3-(5-uracilyl)-propenoic acid.[2] The thio analog **10** was accompanied by traces of **9** and **11**, and the 5-vinyluracil **14** by a very small amount of a material which appeared, from its uv and pmr porperties, to be 5-(1-hydroxyethyl)uracil. The alternative reaction pathways proposed in Scheme VII are strongly supported by the results with *tert*-butyl alcohol. The stronger basicity of the *tert*-butoxide anion *vs.* that of the methoxide[51,52] should promote the abstraction of the allylic proton from the terminal methyl group of **6b** (Scheme VII). Thus in *tert*-butyl alcohol–sodium *tert*-butoxide the formation of **10** (or **14**) (Scheme II) should be favored, as observed. In this system the concentration of species **6c**, which depends in part upon the reverse addition of CH_3O^- to **6b**, should be greatly lowered and the yield of **11** thus reduced, because the addition of the more bulky *tert*-butoxide anion to **6b** is sterically prevented. Further evidence that **11** arises *via* **6c** was obtained by performing the reaction in the system ethanol–sodium ethoxide, in which case a 1:2 mixture (as evidenced by pmr) of 5-(1-methoxyethyl)-2-thiouracil (**11**) and 5-(1-ethoxyethyl)-2-thiouracil was obtained. This demonstrates the reversibility of the alkoxide addition as described in Scheme VII and the influence of the basicity of the alkoxide on the course of the reaction. It should be emphasized that reversible addition ⇄ elimination of alkoxide anion is a feature common to each of the mechanisms in Schemes III, V, and VII. In two instances another common step is the abstraction of an allylic proton and ultimate cyclization (**7c** → **7d**, Scheme V; **6b** ⇄ **6g** ⇄ **10**, Scheme VII). In each of these cases, regardless of the immediate following step, *i.e.*, intramolecular Michael addition (Scheme V) or "rearrangement" of the incipient carbanion to a more stable resonance form (Scheme VII), the initial proton abstraction results in displacement of a methoxide group.

The condensation reactions of trifunctional molecules such as **6** with ureas are being further explored with respect to their general applicability to the synthesis of 5-substituted pyrimidines of biological importance.

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are uncorrected. Pmr spectra were obtained using a Varian A-60 spectrometer with tetramethylsilane as an internal reference. Uv (H_2O, Table I) and infrared spectra were determined with a Unicam SP800A recording spectrophotometer and a Perkin-Elmer Infracord spectrophotometer, respectively. All solvents were removed in a Buchler flash evaporator under reduced pressure, unless otherwise indicated. All solids were dried under

(51) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N. Y., 1968, p 220.

(52) W. K. McEwen, *J. Amer. Chem. Soc.*, **58**, 1124 (1936).

TABLE I

ULTRAVIOLET ABSORPTION PROPERTIES

Compd	Charge	λ_{max}, nm ($\epsilon \times 10^{-3}$)	λ_{min}, nm ($\epsilon \times 10^{-3}$)
2	0	271 (13.8)	246 (3.5)
		228 (9.5)	
12	0	284 (9.3)	243 (1.4)
8	0	275 (14.7)	248 (4.2)
		234 (8.6)	
11		sh 285 (15.1)	240 (3.2)
		274 (15.4)	
		214 (13.9)	
	−1	315 (9.1)	289 (5.7)
		259.5 (11.9)	243.5 (9.0)
		234 (10.4)	219 (8.5)
		209 (11.2)	
	−2	292 (9.1)	279 (8.2)
		260 (12.2)	244 (9.7)
9	0	sh 294 (15.2)	254 (9.9)
		276 (16.8)	230 (13.1)
		238 (13.5)	

reduced pressure over P_2O_5 at suitable temperatures. An Eastman chromagram silica gel sheet was used for tlc and developed as indicated. Composition and homogeneity of liquid samples were monitored by an Aerograph gas chromatograph using a column (0.125 in. i.d. × 100 in. l.) packed with 20% silicon SP-30 on 30/70 Aeropack 30.

Methyl 3-Methoxybutyrate (3).—A solution of 1 g of Na in 40 ml of CH_3OH was added dropwise and with stirring to 100 g (1 mol) of methyl crotonate containing 5 g of *N*-phenyl-2-naphthylamine. The addition was often followed by a brief exothermic reaction and occasional cooling was needed to maintain the temperature at <50°. After overnight stirring the mixture was acidified with 3 ml of glacial acetic acid and submitted to exhaustive distillation under vacuum. An optimum rate of distillation was obtained by slowly raising the temperature of the heating bath from 50 to 90° while gradually reducing the pressure to ~9 mm. The crude product, which contained ~20–25% of starting material, was fractionated in a stainless steel spinning-band column (Nester–Faust) to give 96.8 g (73.5%) of methyl 3-methoxybutyrate: bp 71–72° (41–42 × 10^{-3} mm); ir $\lambda_{max}^{film\ liq}$ 2820 cm^{-1} (symmetrical stretching of methoxyl CH_3[53]) pmr ($CDCl_3$) τ 8.82 (d, 3, J = 6 Hz, CH_3CH–), 6.7 (s, 3, $CHOCH_3$), 6.33 (s, 3, $COOCH_3$). The methylene and methine protons produced a typical ABX spectrum. The AB part (eight lines, 2, J_{AB} = 15 Hz, $-CH_2-$) centered at τ 7.55 and the X part (multiplet, 1, –CH–) centered at τ 6.22.

Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.36; H, 9.20.

Methyl 2-Dimethoxymethyl-3-methoxybutyrate (6).—To a mixture of benzene (25 ml) and sodium (4.6 g, 0.2 mol, cut in small cubes) cooled to 0° in an ice bath, 4.8 g (0.15 mol) of methanol was added dropwise. After stirring for 1 hr at 0°, a mixture of 13.3 g (0.1 mol) of methyl 3-methoxybutyrate and 12 g (0.2 mol) of methyl formate was also added dropwise over 30 min. The temperature of the cooling bath was slowly raised to 8°, where it was maintained for 5 hr and then allowed to reach ambient temperature. After stirring for 72 hr, the reaction mixture (a yellow-orange paste) was again cooled to 0°, 25.2 g (0.2 mol) of dimethyl sulfate was added dropwise over a 3-hr period, and the mixture was then heated at 50° for an additional 3 hr. After cooling the mixture was filtered and the salts were repeatedly washed with benzene (or ether). The combined filtrates (~250 ml) were extracted once with 5% $NaHCO_3$ solution, then with water, and dried over Na_2SO_4. After removal of the solvents below 30°, the residue was distilled in a short path apparatus under high vacuum at a bath temperature of 50–55°. The fraction boiling at 40–44° (5–10 × 10^{-3} mm)[54] was collected. The yield of the product varied between 6.8 and 8 g (~36%). A considerable amount of the polymerized residue remained in the boiling flask: ir $\lambda_{max}^{film\ liq}$ 2820 cm^{-1} (strong, $-OCH_3$[53]); pmr ($CDCl_3$) τ 8.72 (d, 3, J = 6 Hz, CH_3CH–), 6.23 (s, 3, $-COOCH_3$), 6.58 (s, 3, $-CHOCH_3$); signals due to the acetal methoxy groups appear at τ 6.59 and 6.63.

Anal. Calcd for $C_9H_{18}O_5$: C, 52.41; H, 8.80. Found: C, 52.06; H, 8.70.

Reaction of 6 with 2,4-Dinitrophenylhydrazine. Preparation of Pyrazoline Derivatives (13).—An ethanolic solution of 6 was slowly added to a cold solution of 2,4-dinitrophenylhydrazine in 3 *N* HCl. After the solution had stood at room temperature for 24 hr, the yellow precipitated product was collected, repeatedly washed on the filter with 3 *N* HCl (until the washings were colorless) and then water, and dried; it shrinks near 170° and melts to a deep red liquid at 187–188°.

Anal. Calcd for $C_{12}H_{12}N_4O_6$: C, 46.76; H, 3.92; N, 18.17. Found: C, 46.80; H, 3.86; N, 18.15.

The pmr spectrum of the material shows the absence of any ether OCH_3 and the presence of an ester OCH_3. Interestingly, a solution of the material in $CDCl_3$ produces one set of signals, while the spectrum of a solution in DMF-d_6 clearly shows the presence of two sets of similar signals. In the second set the signals of $-COOCH_3$ and $-NCHCH_3$ groups appear, respectively, 4 Hz downfield and 15 Hz upfield from the corresponding ones of the first set. When the solvent (DMF-d_6) was removed (lyophilization) and the pmr spectrum of the residue in CDCl was examined, the signals of the second set were shifted and tended to overlap with the corresponding ones of the first, while the ratio between similar signals of each set remained the same.

Dimethyl (2-Ethylidene-3-methyl)glutarate (5) and Dimethyl 4-Methylisophthalate (7).—The general procedure as described for 6 was used, with the following modifications. Ether (75 ml) and 9.6 g of a 56.5% suspension of NaH were used instead of benzene and sodium. Instead of distilling the crude residue, it was chromatographed on a silica gel G column (100 g) and eluted with 3 l. of petroleum ether (bp 30–60°). Fractions containing the products (as shown by vpc) were pooled, the solvent was removed, and the residue was rechromatographed in a similar manner. Homogeneous fractions were again combined and the solvent was removed, leaving a viscous residue. The residue was chilled for 24 hr, during which time crystals separated. The supernatant was removed with a capillary pipet and dissolved in a small amount of petroleum ether, and the solution was again chilled to yield a second crop of crystals. This procedure was repeated until no more crystalline product could be obtained. The combined crops of crystals and the final supernatant liquid were treated as follows.

Dimethyl 4-Methylisophthalate (7).—This was recrystallized from ether–petroleum ether to give white needles (200 mg): mp 76–77° (subsequent vacuum sublimation did not raise the melting point); pmr ($CDCl_3$) τ 7.35 (s, 3, $-CH_3$), 6.1 [s, 6, $(CO-OCH_3)_2$], 2.69 (d, 1, $J_{5,6}$ = 8 Hz, C_5 H), 1.95 (pair of d, 1, $J_{6,5}$ = 8 Hz, $J_{6,2}$ = 2 Hz, C_6 H), 1.48 (d, 1, $J_{2,6}$ = 2 Hz, C_2 H).

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.80. Found: C, 63.19; H, 5.74.

Dimethyl (2-Ethylidene-3-methyl)glutarate (5).—The supernatant liquid previously mentioned was distilled and a main fraction boiling at 48–49° (85 × 10^{-3} mm) was collected. Pmr ($CDCl_3$) indicated that two isomers were present in an approximate ratio 5 or 6:1. The major isomer produced absorptions at τ 8.81 (d, 3, J = 7 Hz, $CH_3CH<$), 8.16 (d, 3, J = 7 Hz, $CH_3CH=$), 3.2 (q, 1, J = 7 Hz, $CH_3CH=C$). The minor isomer displayed corresponding signals at approximately τ 8.9, 8.1, and 4.0.[55]

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.00; H, 8.10.

An authentic sample of dimethyl 4-methylphthalate was prepared by a modification of a procedure by Bentley and Perkin.[24] A solution of 632 mg (4 mmol) of $KMnO_4$ in 20 ml of H_2O was added to a solution containing 300 mg (2 mmol) of 2,5-dimethylbenzoic acid and 210 mg (2 mmol) of Na_2CO_3 in 5 ml of water, and the resulting mixture was stirred at 60° for 5 hr, then allowed to stand at room temperature overnight. After the mixture was briefly heated on a steam bath, the brown precipitate was removed by filtration and washed several times with hot water. The combined filtrates were acidified to pH <2 with concentrated HCl and chilled. The precipitated crude product, which was

(53) K. Nakanishi, "Infrared Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 36.

(54) The boiling point varies slightly depending upon the rate of distillation.

(55) These values are in agreement with those reported for the cis and trans isomers of dimethyl 2-methylpent-3-ene-1,3-dicarboxylate (*i.e.*, 5): T. Saegusa, Y. Ito, S. Kobayashi, and S. Tomita, *Chem. Commun.*, 273 (1968); M. Ikeda, T. Hirano, and T. Tsuruta, *Tetrahedron Lett.*, 4477 (1972).

contaminated with starting material, was collected and chromatographed on a Sephadex G-10 column (50 cm) eluted with 0.05 M NaH_2PO_4 buffer at pH 7. The product-containing fractions were pooled and evaporated to ~10 ml. The concentrate was acidified to pH <2 with concentrated HCl and extracted continuously with ether. The ether extract was evaporated to a few milliliters and filtered, an equal volume of benzene was added, and the solvents were boiled until the solid product started separating. After cooling, the precipitated product was collected, washed with a small volume of benzene, and dried. The yield of 4-methylisophthalic acid was 225 mg (62%): pmr ($CDCl_3$) τ 7.38 (s, 3, CH_3–), 2.56 (d, 1, $J_{5,6}$ = 8 Hz, C_5 H), 1.97 (pair of d, 1, $J_{6,5}$ = 8, $J_{6,2}$ = 2 Hz, C_6 H), 1.54 (d, 1, $J_{2,6}$ = 2 Hz, C_2 H), −2.40 [broad s, 2, $(-COOH)_2$].

A solution of 180 mg (1 mmol) of the 4-methylisophthalic acid in ~40 ml of CH_3OH was heated under reflux in the presence of 1 ml of Dowex-50 (20–50 mesh, H^+) for 48 hr. The resin was removed by filtration and washed well with methanol, and the combined filtrates were concentrated to dryness. The residue was dissolved in 3 ml of ether, and the solution was filtered. An equal volume of petroleum ether was added to the filtrate. Then the total volume was reduced to ~3 ml on a steam bath and adjusted again to ~6 ml with petroleum ether. After cooling, the precipitated product was collected, washed with a small volume of petroleum ether, and dried. The yield of the dimethyl 4-isophthalate was 155 mg (74.5%) and it melted at 75.5–76.5°. The ir (KBr) and pmr spectra of this product were identical with those of the by-product obtained from the formylation reaction of methyl 3-methoxybutyrate previously described.

5,6-Dihydro-6-methyl-2-thiouracil (2).—To a solution of 920 mg (40 mmol) of Na in ~30 ml of methanol was added 1.67 g (22 mmol) of thiourea, and then 2.64 g (20 mmol) of methyl 3-methoxybutyrate or 2.00 g (20 mmol) of methyl crotonate. The mixture was heated under reflux for 72 hr, the solvent was removed under vacuum, and a solution of 3 ml of glacial acetic acid in 40 ml of cold water was added to the residue. After standing at 0–4° for a few hours the precipitated product was collected, washed with cold water, and dried. The methoxy butyrate gave a higher yield (1.04 g, 36%) than the crotonate (815 mg, 28%). The crude product was either recrystallized directly from methanol or extracted continuously for several days in a small Soxlet extractor with ether (in which it is sparingly soluble). The pure product melts at 220–222°: pmr (pyridine-d_5) τ 8.81 (d, 3, J = 6.5 Hz, $-CH_3$); the C_5 and C_6 proton signals comprise an ABX system; the signal of the AB part is centered at τ 7.49 (seven lines, J_{AB} = 16 Hz); a poorly resolved multiplet, the X part, is centered at approximately τ 6.25.

Anal. Calcd for $C_5H_8N_2OS$: N, 19.43; S, 22.23. Found: N, 19.47; S, 22.25.

The uv absorption properties of 2 are interesting. At pH 7, 5,6-dihydro-6-methyluracil shows only a shoulder at ~210 nm,[56] and thiourea alone exhibits an absorption maximum at 238 nm. However, 5,6-dihydro-6-methyl-2-thiouracil (2) at neutral pH shows two distinct maxima at 271 nm (ϵ 13.8 × 10^3) and 228 (9.5 × 10^3). The absorption at a higher wavelength of 2 is certainly not due to the presence of the monoanion, since its spectrum is essentially unchanged in 20% sulfuric acid.[57] When 2 is treated with aqueous alkali, it is rapidly converted to a material with the uv absorption spectrum of thiourea (*i.e.*, showing λ_{max} at 238 nm), and that transition can be followed spectrophotometrically. Reversal to the original uv absorption was not observed upon acidification of a dilute aqueous solution of the product even after prolonged standing. When this product was charged on a Dowex-50 (H^+) column that was washed with water after an incubation period of 24 hr, the only uv-absorbing fraction obtained exhibited the uv spectrum of the starting material 2.[58] The reverse reaction is extremely slow or inhibited in dilute aqueous solution but proceeds on the matrix of the Dowex-50 resin. Repeated attempts to crystallize the product from a variety of solvent systems failed, although, upon attempted sublimation under vacuum at 80°, the viscous material solidified to give 2, and sublimation proceeded very slowly.

5-Carbomethoxy-4-methyl-3,4-dihydropyrimidin-2-one (12).—A solution of the acetal 6 (1.03 g, 5 mmol) and urea (300 mg, 5 mmol) in 25 ml of methanol containing 0.5 ml of concentrated HCl was heated under reflux for 8 hr. The mixture was taken to dryness, the residue was dissolved in a fresh volume of methanol, and the solution was again taken to dryness. This treatment was repeated several times in order to remove most of the HCl. The final residue was charged on a silica gel G column (80 g, 4 × 14 cm) and 1.5 l. of a mixture of C_6H_6–CH_3OH (9:1) was passed through. The fractions obtained (20 ml each) were checked by tlc using the solvent system C_6H_6–CH_3OH (8:2) and those containing the product were pooled, and the mixture was evaporated to a few milliliters. The solution was filtered and the filtrate was taken to dryness. The residue was dissolved in a small volume of benzene containing a few drops of methanol and sufficient solvent was removed on a steam bath to induce separation of a solid. Crystallization was completed in the cold and the product was collected, washed with a small volume of ether, and dried (430 mg, 50.5%): mp 171–172°; pmr (DMSO-d_6) τ 8.8 (d, 3, J = 6 Hz, CH_3CHN–), 6.35 (s, 3, CH_3O–), 5.81 (eight lines, 1, J = 6, $J_{4,3}$ = 3 Hz, CH_3CHN–), 2.89 (d, 1, $J_{6,1}$ = 6 Hz, =CHN–), 1.10 (d, 1, $J_{3,4}$ = 6 Hz, $-NHCHCH_3$). The N^3 H signal is concealed by that of the C_6 proton.

Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.41; H, 5.92; N, 16.46. Found: C, 49.47; H, 5.99; N, 16.43.

Condensation of 6 with Thiourea in Methanol–Sodium Methoxide. Preparation of 5-(1-Methoxyethyl)-2-thiouracil (11), **5-(1-Thiocarbamylaminoethyl)-2-thiouracil** (9), **5-Vinyl-2-thiouracil** (10), **and 5-Dimethoxymethyl-5,6-dihydro-6-methyl-2-thiouracil** (8).—To a solution of 460 mg (20 mmol) of Na in ~15 ml of methanol was added 836 mg (11 mmol) of thiourea followed by 2.06 g (10 mmol) of the acetal 6. The mixture was heated under reflux for 72 hr, then was taken to dryness, and the residue was dissolved in a small volume of cold water. The resulting solution was passed through a column (i.d. 1 cm) of Amberlite IRC-50 (H^+), 20–50 mesh, 20 ml. The column was heated to 40–50° while the resin was washed with water (3 l.) until the eluate showed negligible uv absorption. The combined eluates were taken to dryness and the residue was washed once with a small volume of benzene, which was discarded. The crude product was applied on a silica gel G column (80 g, 4 × 15 cm), which was developed first with 2 l. of C_6H_6–EtOAc (8:2) and then with C_6H_6–EtOAc–CH_3OH (8:1.5:0.5), and finally with 1 l. of C_6H_6–CH_3OH (8:2). Each of the 20-ml fractions collected was analyzed by tlc (C_6H_6–CH_3OH, 8:2).[59] The products emerge in the order **10**, **8**, **11**, and **9**.

5-Vinyl-2-thiouracil (10).—Fractions 22–31 were pooled, the solvent was removed, and the residue was triturated with a small volume of benzene. The remaining solid was dissolved in methanol, and the solution was treated with Norit and then filtered through a pad of Celite. The volume of the filtrate was reduced by boiling on a steam bath and then a few milliliters of benzene was added. This was repeated several times until crystals began to form. The mixture was cooled and the product was collected, washed once with benzene, and dried (65 mg). It slowly decomposed above 170° without melting. The pmr (DMSO-d_6) spectrum of the side chain showed a pattern similar to that of 5-vinyluracil:[2] for H_A, τ 4.8 (pair of d, J_{AB} = 3.5, J_{AC} = 10 Hz); H_B, 3.98 (pair of d, J_{BC} = 17, J_{BA} = 3.5 Hz); H_C, 3.52 (pair of d, J_{CB} = 17, J_{CA} = 10 Hz).

Anal. Calcd for $C_6H_6N_2OS$: N, 18.17; S, 20.79. Found: N, 18.13; S, 20.78.

5,6-Dihydro-5-dimethoxymethyl-6-methyl-2-thiouracil (8).—Fractions 32–44 were combined, the solvent was removed under vacuum, and the solid residue was recrystallized from methanol (after treatment with Norit) to give 75 mg of a product with mp 208–210°: pmr (DMSO-d_6) τ 8.92 (d, 3, J = 6.5 Hz, CH_3CH–), 7.4 (multiplet, 1, C_5 H), 6.78 [s, 6, $(-OCH_3)_2$], 6.47 [multiplet, 1, $-CH(OCH_3)_2$], 5.5 (d, 1, J = 6.5 Hz, CH_3CHN–).

Anal. Calcd for $C_8H_{14}N_2O_3S$: N, 12.83; S, 14.69. Found: N, 12.83; S, 14.71.

5-(1-Methoxyethyl)-2-thiouracil (11).—Fractions 51–85 were combined and then taken to dryness. The residue was triturated with a small volume of benzene, and the supernatant was discarded. The remaining solid (440 mg) was dissolved in benzene containing sufficient methanol (several drops) to bring about

(56) For comparison 6-methyluracil shows λ_{max} 260 nm (ϵ 9.5 × 10^3) and λ_{min} 230 (1.8 × 10^3).

(57) H_0 = −1.06. C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Amer. Chem. Soc.*, **91**, 6654 (1969).

(58) The crude mixture can be resolved readily on a silica gel G column which is eluted with the system acetone–water (95:5), or on a Sephadex G-10 column with 0.025 M NaH_2PO_4 buffer at pH 7.

(59) If the solvents were allowed to evaporate slowly over several days until the volume of the fractions was reduced by one half, the products crystallized and the determination of the range for each component by tlc was facilitated.

solution. The solvent was evaporated on a steam bath until the solution was turbid. After chilling, the deposited crystals were collected and dried. The product melted at 168–169°: pmr (DMSO-d_6) τ 8.75 (d, 3, J = 6.5 Hz, $-CHCH_3$), 6.82 (s, 3, $-OCH_3$), 5.8 (pair of q, 1, $J_{1',2'}$ = 6.5 Hz, allylic coupling $J_{1',6}$ = 1 Hz), 2.85 (d, 1, $J_{6,1'}$ = 1 Hz); pK_a's 7.80 ± 0.04 and 13.0 ± 0.2.[60]

Anal. Calcd for $C_7H_{10}N_2O_2S$: N, 15.04; S, 17.22. Found: N, 14.96; S, 17.27.

5-(1-Thiocarbamylaminoethyl)-2-thiouracil (9).—Fractions 117–128 were allowed individually to evaporate slowly to about 5 ml (25% of the original volume), when rosettes of crystals deposited. In the last fractions the rosettes were mixed with some amorphous solid. Each of the latter fractions was briefly mixed with a Vortex Mixer, and the turbid solvent was removed with a pipet. The isolated rosettes were collected and then added to the combined total contents of the remaining fractions. The resulting mixture was dried, the residue was dissolved in hot methanol, and the solution was filtered through a thin pad of Norit deposited on Celite. The clear filtrate was evaporated under vacuum to a few milliliters and enough benzene was added to induce turbidity. The resulting mixture was allowed to stand at room temperature in an open flask which permitted slow evaporation of the solvent. After 3 days a crystalline material had deposited. A few drops of benzene were added, causing the supernatant to become turbid. After standing overnight the deposited crystals were collected, washed with benzene, and dried. The yield of the product was 400 mg, and it melted at 202–203°: pmr (DMSO-d_6) τ 8.7 (d, 3, J = 7 Hz, $-CHCH_3$), 5.05 (multiplet, 1, $-NCHCH_3$), 2.92 (s, 2, $-NH_2$), 2.85 [s, 1, $-NHC(=S)-NH_2$], 2.25 (d, 1, $J_{6,1}$ = 8 Hz).

Anal. Calcd for $C_7H_{10}N_4OS_2$: N, 24.33; S, 27.84. Found: N, 24.28; S, 27.82.

The combined yield for products **10**, **8**, **11**, and **9** was 54%.

5-[1-(Methylthio)carbamylimino)ethyl]-2-methylthiouracil (15).—The pyrimidine **9** (230 mg, 1 mmol) was dissolved in 4 ml of water containing 2.2 mmol of NaOH, 312.5 mg (2.2 mmol) of CH_3I was added, and the mixture was stirred at room temperature for several days. The white precipitate was collected, washed with cold water, and dried. It weighed 200 mg (77%) and after recrystallization from methanol it melted at 186–188°. Pmr (DMSO-d_6) indicates the presence of both cis and trans isomers. For the predominant one the nmr values (DMSO-d_6) are 8.57 (d, 3, J = 7 Hz, $-CHCH_3$), 7.66 and 7.52 (CH_3S- groups), 5.22 (q, 1, J = 7 Hz, $-NCHCH_3$), 2.3 (s, C_6H).

Anal. Calcd for $C_9H_{14}N_4OS_2$: N, 21.68; S, 24.82. Found: N, 21.73; S, 24.79.

Condensation of 6 with Urea (or Thiourea) in *tert*-Butyl Alcohol–Sodium *tert*-Butoxide. 5-Vinyluracil (14).—To ~200 ml of *tert*-butyl alcohol containing 1.38 g (60 mmol) of Na was added 3.6 g (60 mmol) of urea, the mixture was heated to boiling, and 6.18 g (30 mmol) of the acetal **6** was added. Heating under reflux with stirring continued for 48 hr, the solvent was then removed, the residue was dissolved in cold water, and the solution was neutralized batchwise with 50 ml of Amberlite IRC-50 (H^+). The supernatant was decanted and saved and the exchange resin was washed in a column with warm (60°) water until the uv absorption of the washings was negligible (~3 l.). The combined washings were filtered and the filtrate was evaporated to ~100 ml and then chilled. The separated solid was collected, washed once with water, and dried (825 mg). An additional crop (380 mg) was obtained from the mother liquors. The total yield averaged ~29%. The crude product was purified on a silica gel G column (100 g, 4 × 18 cm) by elution first with 1.5 l. of C_6H_6–EtOAc (8:2), then with 2 l. of C_6H_6–CH_3OH (9:1), followed by 1 l. of C_6H_6–CH_3OH (8:2). The fractions containing the product were pooled, the solvent was removed, and the residue was recrystallized from methanol. The pure product was collected, washed once with ether, and then dried. Its melting point and uv absorption properties were identical with those reported.[2]

Alternatively, the crude product could be purified on a Dowex-50 (H^+) column which was washed with water. The elution had to be completed within the same day because 5-vinyluracil is unstable on the Dowex-50 resin. A small quantity of a second product was isolated from such a Dowex-50 column and the pmr and uv spectra suggested it to be 5-(1-hydroxyethyl)uracil.

5-Vinyl-2-thiouracil (10).—A mixture of 80 ml of *tert*-butyl alcohol containing 460 mg (20 mmol) of Na and 1.52 g (20 mmol) of thiourea was heated to boiling, then 2.06 g (10 mmol) of the acetal **6** was added, and boiling with stirring was continued for 72 hr. After the solvent had been removed, the residue was dissolved in water and the solution was passed through a column of Amberlite IRC-50 (H^+, 20 ml) which was exhaustively washed well with water (3 l.). The combined eluates were evaporated to dryness and the residue was dissolved in methanol. The solvent was again removed and the residue was applied to a silica gel G column (100 g, 4 × 14 cm) which was developed with 3 l. of C_6H_6–EtOAc (8:2). The fractions containing the product were pooled and the solvent was removed. The residue was first triturated with a small volume of benzene, and recrystallized as described previously for the same compound. The yield was 270 mg (17.5%).

Registry No.—**1**, 18707-60-3; **2**, 6300-93-2; **3**, 3136-17-2; (*E*)-**5**, 16657-04-8; (*Z*)-**5**, 16657-03-7; **6**, 39541-78-1; **7**, 23038-61-1; **7** free acid, 3347-99-7; **8**, 39550-26-0; **9**, 39550-27-1; **10**, 39550-28-2; **11**, 39550-29-3; **12**, 39541-81-6; **13**, 39526-93-7; **14**, 37107-81-6; (*E*)-**15**, 39541-83-8; (*Z*)-**15**, 39541-84-9; methanol, 67-56-1; methyl formate, 107-31-3; 2,4-dinitrophenylhydrazine, 119-26-6; thiourea, 62-56-6; urea, 57-13-6; 5-(1-hydroxyethyl)uracil, 39541-85-0.

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(60) The pK_a's were determined by methods described spectrophotometrically in 0.01 *M* buffers with a Beckman DU spectrophotometer.[61]

(61) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962, p 69.

Synthesis of 2-Amino-L-histidine and 2-Aminohistamine

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While aryldiazonium coupling to *N*-benzoylhistidine esters leads almost entirely to 2,4-bisarylazo derivatives, coupling in the *N*-acetyl series leads predominantly to the 2-arylazo derivative. Similarly, *N*-acetylhistamine couples predominantly at C-2. Catalytic hydrogenolysis of the 2-arylazo derivatives, followed by acid hydrolysis to cleave the side-chain acetamido and ester groups, produced the desired 2-amino-L-histidine and 2-aminohistamine. Success in the synthesis and isolation of these new histidine analogs is dependent on careful chromatographic purification (silicic acid) of the 2-arylazo derivatives. These 2-aminoimidazoles are stable to acid, alkali, and oxygen. Carboxyl derivatives of 2-aminohistidine are hydrolyzed by trypsin, suggesting that the enzyme recognizes the structural similarity between 2-aminohistidine and arginine.

Syntheses of 4-fluorohistamine and of 4-fluorohistidine, based on a photochemical route to ring-fluorinated imidazoles, have been reported from this laboratory recently.[2] Initial studies on the enzymatic and *in vivo* properties of these analogs of histamine and of histidine provided results of sufficient interest to stimulate our pursuit of the corresponding 2-fluoro series. Since we had already obtained 2-fluoroimidazole from 2-aminoimidazole (by irradiation of the corresponding diazonium ion in fluoroboric acid solution),[2] we undertook the synthesis of some 4-substituted 2-aminoimidazoles which might serve as precursors of 2-fluorohistamine and of 2-fluorohistidine, as well as of other members of the series. Since these syntheses proved largely unfeasible, and since the intermediates ultimately used,[3] 2-aminohistamine and 2-aminohistidine, proved to be of considerable biochemical interest in their own right, this report is concerned with the preparation of the latter compounds, as well as with some of the obstacles encountered in general approaches to 2-aminoimidazoles.

In contrast to the very unstable 4-aminoimidazoles, the isomeric 2-aminoimidazoles generally exhibit a high degree of stability.[4,5] Despite this feature, relatively few members of the latter series have been described, and most of these have either a C-aryl substituent or an alkyl substituent at a ring nitrogen atom.[4,6] Our initial efforts were directed toward the synthesis of a 2-aminoimidazole carrying a group such as hydroxymethyl, carboxaldehyde, or carbalkoxy at C-4. Condensation of cyanamide[6] or of *S*-methylisothiourea[6b] with esters of *C*-formylglycine, and of guanidine (or its derivatives)[7] with dihydroxyacetone, ethyl hydroxypyruvate, or ethyl bromopyruvate,[8] invariably led to products other than imidazoles.[9] Attempts to dehydrogenate[10] 2-amino-2-imidazoline-4-carboxylic acid[11] failed, as did efforts to formylate 2-acetaminoimidazole at C-4.[12]

One remaining option was reinvestigation of the classical route to 2-aminoimidazoles, the reduction of 2-arylazo derivatives. While this route had been successful for the synthesis of some simple C-alkylated (or arylated) 2-aminoimidazoles,[13] previous efforts to apply the technique to histidine[14] and to histamine[14,15] failed. This approach was handicapped by reports that aryldiazonium coupling to α-*N*-benzoylhistidine methyl ester results in formation of bisarylazo derivatives almost exclusively,[14,16,17] a result which we confirmed. Variation in reactant ratios, experimental conditions, or in the nature of the aryldiazonium ion failed to repress bis coupling. Surprisingly, however, the principal coupling product of α-*N*-acetylhistidine methyl ester (**1**) proved to be a monoarylazo derivative. Careful chromatography of the crude precipitate of arylazo derivatives on silicic acid produced three homogeneous fractions: the 2-arylazo (**4**, 73–82%) and 4-arylazo (**3**, 13–18%) derivatives, as well as the 2,4-bis derivative (**5**, 5–9%). These results are based on the use of 1 equiv of arylamine. The composition of the precipitate formed during the reaction is not affected significantly by variation in the nature of the diazonium ion or in pH (7.5–9.5); rapid precipitation of the monoazo derivative may be critical, however, in repression of bis coupling.[18] With α-*N*-acetylhistidine, bis coupling again became the major pathway, presumably because the initial product remained in

(1) Associate in the Visiting Program, USPHS, 1971–1973.

(2) K. L. Kirk and L. A. Cohen, *J. Amer. Chem. Soc.*, **93**, 3010 (1971); *ibid.*, in press.

(3) Synthesis in the 2-fluoroimidazole series will be reported separately.

(4) (a) K. Hofmann, "Imidazole and Its Derivatives," Interscience, New York, N. Y., 1953, p 141; (b) E. S. Schipper and A. R. Day in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1957, p 223; (c) A. F. Pozharskii, A. D. Garnovskii, and A. M. Simonov, *Usp. Khim.*, **35**, 261 (1966); *Russ. Chem. Rev.*, **35**, 125 (1966).

(5) 4-Aminoimidazoles are stable only in the presence of a C-5 substituent capable of resonance interaction with the amino group (carbonyl, sulfonyl, nitro groups, etc.). Whether such a substituent at C-2 confers comparable stability on a 4-amino group has yet to be determined.

(6) For leading references, see (a) A. Lawson, *J. Chem. Soc.*, 307 (1956); (b) B. T. Storey, W. W. Sullivan, and C. L. Moyer, *J. Org. Chem.*, **29**, 3118 (1964); (c) G. C. Lancini and E. Lazzari, *J. Heterocycl. Chem.*, **3**, 152 (1966); (d) G. C. Lancini, E. Lazzari, V. Arioli, and P. Bellani, *J. Med. Chem.*, **12**, 775 (199).

(7) (a) T. Pyl, S. Melde, and H. Beyer, *Justus Liebigs Ann. Chem.*, **663**, 108 (1963); (b) T. Pyl, H. Lahmer, and H. Beyer, *Chem. Ber.*, **94**, 3217 (1961); (c) H. Brederick, R. Sell, and F. Effenberger, *ibid.*, **97**, 3407 (1964); (d) I. Iwai and Y. Yura, Japanese Patent 24,885 (1963); *Chem. Abstr.*, **60**, 4154 (1964).

(8) Ethyl imidazole-4-carboxylate is obtained in 30% yield from the reaction of ethyl bromopyruvate and formamide (L. A. Cohen, unpublished results).

(9) In reactions involving these trifunctional systems, it is likely that six-membered ring formation occurs preferentially.

(10) W. Ried and R. Lantzsch, *Chem. Ber.*, **102**, 378 (1969); P. K. Martin, H. R. Matthews, H. Rapaport, and G. Thyagarajan, *J. Org. Chem.*, **33**, 3758 (1968).

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(13) R. G. Fargher and F. L. Pyman, *J. Chem. Soc.*, **115**, 217 (1919); F. L. Pyman and L. A. Ravold, *ibid.*, **117**, 1426 (1920); R. Burtles and F. L. Pyman, *ibid.*, **127**, 2012 (1925); A. de Cat and A. van Dormael, *Bull. Soc. Chim Belg.*, **59**, 573 (1950); A. Kreutzberger, *J. Org. Chem.*, **27**, 886 (1962).

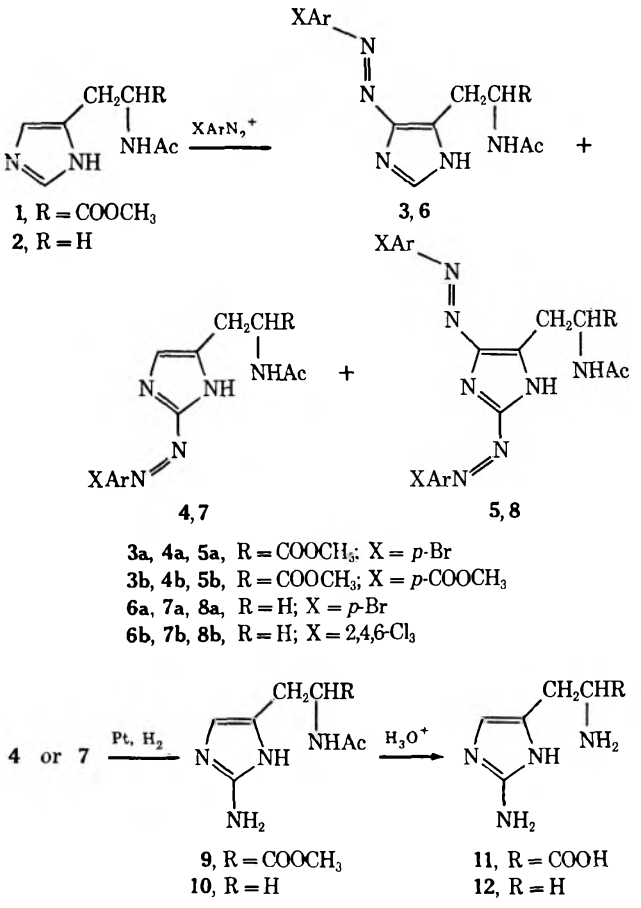
(14) W. Diemair and H. Fox, *Ber.*, **71**, 2493 (1938).

(15) L. Kesztyüs, *Arch. Exp. Pathol. Pharmakol.*, **205**, 287 (1948).

(16) S. Koshimura, *Jap. J. Exp Med.*, **21**, 343 (1951).

(17) Diazonium coupling to histidine itself produces at least seven products: W. Diemair and H. Fox, *Biochem. Z.*, **298**, 38 (1938).

(18) We have no obvious explanation for the striking difference in behavior between the *N*-acetyl- and *N*-benzoylhistidine esters, although rate of precipitation may be a factor.



solution. Assignments of structure to the isomeric monoarylazo derivatives were based on their nmr spectra (Table I),[19] and on the fact that each species assigned a 2-arylazo structure produced a *stable* aminoimidazole. Visible spectra for the arylazo compounds are given in Table II; it is interesting and useful to note that λ_{max} for each 2-arylazo derivative is consistently 30–40 nm higher than that for its 4-arylazo isomer.

TABLE I
NMR SPECTRA OF IMIDAZOLE DERIVATIVES[a]

Compd	δ, ppm H2	δ, ppm H4
1	7.58 (8.76)	6.85 (7.41)
2	7.56 (8.73)	6.83 (7.36)
3a	7.83	
4a		7.20
3b	7.86	
4b		7.30
6a	7.83 (8.57)	
7a		7.26 (7.36)
6b	7.87 (8.45)	
7b		7.35 (7.45)
9		6.56
10		6.23

[a] All spectra were recorded on a Varian A-60 spectrometer in DMSO-d_6 solution; values in parentheses refer to CD_3COOD solution.

(19) The chemical shift of a proton at C-2 invariably appears further downfield than that of a proton at C-4: G. L. Schmir, W. M. Jones, and L. A. Cohen, *Biochemistry*, **4**, 539 (1965).

Although aryldiazonium coupling to histamine and to its α-*N*-acyl derivatives had been reported to produce principally monoarylazo derivatives,[14,15] the heterogeneous composition of these products and their resistance to purification by direct crystallization had not been recognized. In parallel with our results with **1**, α-*N*-acetylhistamine (**2**) afforded, after silicic acid chromatography of the crude precipitate of coupling products, 87% of the 2-arylazo derivative (**7a**), 5% of the 4-arylazo derivative (**6a**), and 8% of the 2,4-bisarylazo derivative (**8a**). Coupling of **2** with 2,4,6-trichlorophenyldiazonium ion produced a significantly greater fraction of the 4-arylazo derivative (34%). Since the aryldiazonium ion shows a decided preference for C-2 (when positions 2 and 4 are both available), as is apparent from the results above as well as from numerous earlier studies,[4] the behavior of the trichlorophenyldiazonium ion is surprising and warrants further study.

Prior to reductive cleavage of the azo linkage, it is essential that the 2-arylazo derivative be as free as possible of contamination by either the 4-arylazo or the 2,4-bisarylazo derivative. Reduction at the 4-arylazo site leads to unstable 4-aminoimidazoles, which are subject both to air oxidation and to hydrolytic imidazole ring cleavage.[14,15] Separation of the highly polar products of these decompositions from the equally polar 2-aminoimidazoles is tedious and unnecessary. Accordingly, exhaustive purification at the arylazo stage is preferable to that at any subsequent step.

The reagent most generally used for reductive cleavage of arylazo compounds, stannous chloride, proved only partially satisfactory for the present cases; although the desired aminoimidazoles were formed, benzidine rearrangements and other side reactions[13] served to complicate purification and to reduce yields sizeably. Reduction with sodium dithionite proved even less satisfactory, leading to water-soluble products (possibly sulfinic or sulfonic acids). The desired 2-aminoimidazoles (**9**, **10**) were obtained, however, by simple platinum-catalyzed hydrogenolysis, cleanly and in good yield. The side-chain acetamido and ester groups were cleaved by acid hydrolysis, resulting in the formation of the new histidine analogs 2-amino-L-histidine (**11**) and 2-aminohistamine (**12**). Neither compound gave evidence of instability in acid or alkali, or upon exposure to air. Both compounds give positive Pauly tests for the imidazole ring, and positive Sakaguchi tests for the guanidine moiety. On the amino acid analyzer, 2-aminohistidine coincides with arginine in its retention time.

The realization that 2-aminohistidine may be viewed as a cyclic analog of arginine led us to consider its derivatives as substrates for trypsin. Indeed, trypsin readily cleaves the ester bond in **9**, and liberates ammonia from α-*N*-acetyl-2-aminohistidineamide. In addition to implications regarding the geometry of the active site of trypsin, these observations suggest the possibility of creating a new site for the tryptic cleavage of polypeptides and proteins.[20] The behavior of these analogs of histamine and of histidine toward other enzymes, as well as their pharmacological properties, is under investigation.

(20) Studies in these directions are in progress and will be reported separately.

TABLE II

PHYSICAL AND ANALYTICAL DATA

Compd	Yield,[a] %	Mp, °C	S[b]	λmax, nm[c] (log ε)	Formula	Calcd, % C	H	N	Br/Cl	Found, % C	H	N	Br/Cl
3a	13	138–140	B	354 (4.39)	$C_{15}H_{16}N_5O_3Br$	45.70	4.09	17.76	20.27	45.34	4.20	17.40	19.53
4a	82	173–175	B	387 (4.41)	$C_{15}H_{16}N_5O_3Br$	45.70	4.09	17.76	20.27	45.89	4.15	17.80	20.18
5a	5	155–158	C	428 (4.44)	$C_{21}H_{19}N_7O_3Br_2$	43.70	3.32	16.99	27.68	43.40	3.38	16.63	27.34
3b	18	132–133	E	358 (4.45)	$C_{17}H_{19}N_5O_5 \cdot H_2O$	52.17	5.41	17.89		52.27	5.32	18.19	
4b	73	187–188	E	388 (4.44)	$C_{17}H_{19}N_5O_5$	54.69	5.13	18.76		54.60	5.13	18.70	
5b	9	150–151	C	435 (4.49)	$C_{25}H_{25}N_7O_7$	56.07	4.71	18.31		55.83	4.82	17.89	
6a	5	214–215[d]	C	353 (4.37)	$C_{13}H_{14}N_5OBr$	46.44	4.20	20.83	23.77	46.14	4.08	20.93	23.99
7a	87	221–223[d]	C	388 (4.46)	$C_{13}H_{14}N_5OBr$	46.44	4.20	20.83	23.77	45.77	4.14	20.66	23.66
8a	8	225[d]	C	427 (4.47)	$C_{19}H_{17}N_7OBr_2$	44.04	3.31	18.92	30.65	43.81	3.21	19.00	30.99
6b	34	203–204	C	327 (4.27)	$C_{13}H_{12}N_5OCl_3$	43.30	3.36	19.42	29.49	42.73	3.29	19.39	29.21
7b	55	189–190	C	365 (4.33)	$C_{13}H_{12}N_5OCl_3$	43.30	3.36	19.42	29.49	42.94	3.15	19.46	28.84
8b	11	203–204	C	385 (4.23)	$C_{19}H_{13}N_7OCl_6$	40.17	2.31	17.26	37.45	39.39	2.20	16.95	37.79
9		183–184	EE		$C_9H_{14}N_4O_3 \cdot 2H_2O$	41.21	6.92	21.36		41.20	6.79	21.14	
10[e]		220–227[d]	E		$C_{13}H_{15}N_7O_8$	39.30	3.81	24.68		39.15	3.89	24.94	
11			MA		$C_6H_{10}N_4O_2 \cdot 2HCl$	29.64	4.98	23.05		29.56	5.16	23.21	
12[f]		220–223[d]	E		$C_{17}H_{16}N_{10}O_{14}$	34.94	2.76	23.97		35.23	2.95	24.09	

[a] Calculated as weight per cent of total material recovered after silica gel chromatography. [b] Solvents for crystallization: B, benzene; C, chloroform; E, 95% ethanol; EE, ethanol–ether; MA, methanol–acetonitrile. [c] Measured in ethanol. [d] Decomposition. [e] Crystallized and analyzed as picrate. [f] As dipicrate.

Experimental Section[21]

α-*N*-Acetyl-L-histidine Methyl Ester (1).—Dry hydrogen chloride was passed into a stirred solution of 12 g (0.056 mol) of *N*-acetyl-L-histidine (Sigma or Aldrich Chemical Co.) in 500 ml of methanol. Introduction of hydrogen chloride was continued for 10 min, and the solvent was removed at reduced pressure (without heat). To the residual oil was added 50 ml of saturated aqueous sodium bicarbonate and an additional 8 g of solid sodium bicarbonate, to produce a final pH of 8.5–9. The mixture was extracted with three 50-ml portions of chloroform, and the combined extracts were dried (Na_2SO_4) and evaporated to give 6.4 g (54%) of colorless, crystalline material. The product was recrystallized from ethyl acetate to give 4.3 g of 1 as needles, mp 124–125°.

Anal. Calcd for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.90. Found: C, 50.89; H, 6.30; N, 19.67.

More prolonged contact of *N*-acetylhistidine with hydrogen chloride, or the use of heat during evaporation of the solvent, resulted in partial loss of the acetyl group. Acetylation of L-histidine methyl ester proved an even less effective procedure.

α-*N*-Acetyl-2-(*p*-bromophenylazo)-L-histidine Methyl Ester (4a).—A solution of 1.44 g (0.021 mol) of sodium nitrite in 20 ml of water was cooled to 0–2° and was added gradually to a stirred, ice-cold solution of 3.44 g (0.02 mol) of *p*-bromoaniline in 100 ml of 2.3 *N* hydrochloric acid. The solution of diazonium salt was stored at ice temperature for 40 min and was then added gradually to a stirred, ice-cold solution of 4.22 g (0.02 mol) of α-*N*-acetyl-L-histidine methyl ester (1) in 200 ml of 0.2 *M* sodium carbonate. The mixture was refrigerated for 2 hr and the yellow-orange precipitate was collected and dried (6.0 g). A solution of 3.78 g of the crude product in the minimum volume of chloroform–methanol (15:1) was applied to a column of silicic acid (600 g, 100 mesh), and the column was eluted with chloroform–methanol (15:1). The mixture of azo compounds was resolved into three bands: the fastest moving consisted of 147 mg of dark red crystals, mp 155–158° ($CHCl_3$), which were identified as the bis product **5a** by nmr (Table I) and by elemental analysis (Table II); the second fraction consisted of 2.6 g of bright yellow crystals, mp 173–175° (benzene), which were identified as the 2-arylazo derivative **4a** by nmr and mass spectra and by elemental analysis; the third fraction consisted of 406 mg of light yellow crystals, mp 138–140° (benzene), which were identified as the 4-arylazo derivative **3a**.

When this diazonium coupling reaction was repeated with *N*-benzoyl-L-histidine methyl ester, only the bis adduct could be detected chromatographically and was isolated as orange crystals, mp 136–137° (acetone).

Anal. Calcd for $C_{26}H_{21}O_3N_7Br_2$: C, 48.84; H, 3.31; N, 15.34; Br, 25.00. Found: C, 48.42; H, 3.49; N, 14.94; Br, 24.44.

For the *p*-carbomethoxyphenyl series **3b–5b**, the diazonium salt was added to a solution of 1 in 0.01 *M* sodium tetraborate, the pH being maintained at 9–9.5 by addition of 1 *N* sodium hydroxide. Physical and analytical data for the coupling products, separated by silicic acid chromatography, are given in Table II.

α-*N*-Acetyl-2-(*p*-bromophenylazo)histamine (7a).—Using a procedure analogous to that for coupling with 1, 9.30 g (0.06 mol) of α-*N*-acetylhistamine (California Biochemical Co.) was coupled with the diazonium salt obtained from 10 g of *p*-bromoaniline. The crude orange-red product, 17.0 g, was resolved into three fractions by chromatography on 900 g of silicic acid (eluent, chloroform–methanol, 15:1). The coupling products were eluted in the same order as in the case of the histidine derivatives; their properties are summarized in Table II.

A similar procedure was used for coupling with 2,4,6-trichloroaniline. The results differed from those above in that the per cent by weight of **6b** was significantly greater than that of **6a**.

α-*N*-Acetyl-2-amino-L-histidine Methyl Ester (9).—A suspension of 5.0 g (0.013 mol) of **4b** in 200 ml of absolute ethanol containing 0.5 g of platinum oxide was subjected to catalytic hydrogenation at ambient temperature and at an initial hydrogen pressure of 40–45 psi (Paar bomb). A hydrogen pressure of 30–40 psi was maintained throughout the reduction process. After the reaction mixture had been shaken overnight, solution was complete; an additional 0.5 g of platinum oxide was added; and reduction was continued for an additional 18 hr. The catalyst was removed by filtration and the solvent was evaporated *in vacuo*. The residual material was dissolved in 100 ml of water, the solution was filtered from a brown precipitate, and the filtrate was extracted with three 100-ml portions of ether. The aqueous layer was evaporated, with minimal heat, to give 2.88 g of yellow-brown crystals (contaminated with resinous material). The crude product was dissolved in 35 ml of ethanol and 80 ml of ether was added. This turbid solution was refrigerated overnight to give 1.43 g of almost colorless, crystalline material, mp 166–169°. Following recrystallization from ethanol–ether, a colorless, crystalline sample of **9** (dihydrate) was obtained, mp 183–184°

The *p*-bromophenylazo derivative **4a** was subjected to a similar hydrogenolysis procedure. The aryl–bromine bond was also cleaved, leading to the hydrobromide of **9**. In an attempt to obtain the free base by ion-exchange chromatography, the methyl ester group of **9** was partially lost during the ammonia elution step. For direct conversion of **4** to **11** (without isolation of **9**), this incident is of little consequence.

2-Amino-L-histidine Dihydrochloride (11 2HCl).—A solution of 360 mg of **9** in 10 ml of 6 *N* hydrochloric acid was heated on

(21) Microanalyses, nmr spectra, and mass spectra were provided by the Microanalytical Services and Instrumentation Section of this laboratory, under the direction of Dr. D. F. Johnson. Homogeneities of all compounds were confirmed by tlc; identities of all compounds, except bisarylazo derivatives, were checked by mass spectroscopy. Under the conditions necessary for their volatilization, the latter compounds decomposed without appearance of a parent ion. All melting points are uncorrected.

steam for 20 hr. The solvent was evaporated *in vacuo*, the residue was dissolved in 10 ml of water, and the solvent was again evaporated; this process was repeated twice more, and the crystalline residue was twice recrystallized from methanol–acetonitrile to give **11** as the dihydrochloride, $[\alpha]^{25}D$ −7.7 (*c* 1.4, H_2O), −13.4 (c 1, 0.2 *M* acetate buffer, pH 5).

α-*N*-Acetyl-2-aminohistamine (**10**).—A suspension of 5.7 g of **7a** in 200 ml of ethanol was subjected to catalytic hydrogenation, as described above for **4b**. Following removal of the catalyst, the solvent was evaporated *in vacuo* and the residual material was dissolved in 100 ml of water. The solution was extracted with three 100-ml portions of ether and the aqueous layer, containing **10** as its hydrobromide, was applied to a column of Dowex 50W. The column was eluted with dilute ammonium hydroxide, and the effluent was evaporated to dryness. The residual oil was dissolved in ethanol, the solution was decolorized partially with Norit, and the solvent was removed to give 2.3 g of a red-brown, noncrystalline solid. This material could not be crystallized and **10** was characterized as its picrate (Table II).

2-Aminohistamine (**12**).—A solution of 1.0 g of **10** in 50 ml of 6 *N* hydrochloric acid was heated on steam for 14 hr. The solvent was removed *in vacuo;* to the residual oil was added 50 ml of ethanol and the solvent was evaporated, the process being repeated. The residual oil was dissolved in 100 ml of ethanol, the solution was decolorized with Norit, and the solvent was removed to give 750 mg of a colorless, noncrystalline solid. The amine **12** was characterized as its dipicrate, mp 200–223° dec (95% ethanol).

Registry No.—**1**, 36097-48-0; **3a**, 39037-16-6; **3b**, 39037-17-7; **4a**, 39037-18-8; **4b**, 39004-81-4; **5a**, 39037-19-9; **5b**, 39037-20-2; **6a**, 39050-06-1; **6b**, 39050-07-2; **7a**, 39050-08-3; **7b**, 39050-09-4; **8a**, 39050-10-7; **8b**, 39050-11-8; **9**, 39037-21-3; **10** picrate 39050-12-9; **11**, 39037-22-4; **11** 2HCl, 39037-23-5; **12**, 39050-13-0; **12** dipicrate, 39050-14-1; *N*-acetyl-L-histidine, 2497-02-1; *p*-bromoaniline, 106-40-1; α-*N*-acetylhistamine, 673-49-4.

A Total Synthesis of Camptothecin and Deethyldeoxycamptothecin[1]

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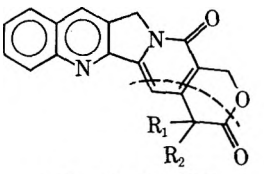
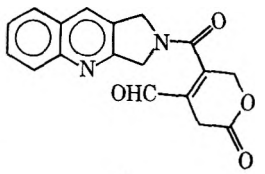
The synthesis of the plant antitumor agent camptothecin, is described. More significantly, the synthesis leads to the pentacyclic lactone **2** in preparative quantities suitable for further study and modification. The scheme involves conversion of the readily available amine **8** to an oxazine amide **7**, which underwent Michael addition with the unsaturated ester **26** leading to the completely functionalized precursor **27**. Borohydride reduction to the tetrahydro-1,3-oxazine **28** followed by cleavage to the aldehyde **29** produced, after borohydride reduction, the hydroxy ester **30**. Acylation of the latter afforded the acetate derivative **41** (R = Me), which was stable to dioxolane cleavage ($BF_3 \cdot Et_2O$) and led to the aldehyde **42** (R = Me). Cyclodehydration of the aldehyde to the pyrrole nucleus gave the dihydropyridone **43** (R = Me), which was aromatized with DDQ to the appropriate pyridone system **45**. Acid hydrolysis then produced the pentacyclic lactone **2** ($R_1 = R_2 = H$), which was converted to racemic camptothecin. A variety of interesting side reactions were encountered during the study, resulting in novel heterocyclic ring systems (*e.g.*, pyrrole oxazines **21**, and *N*-alkyl pyrroles **25**). Certain model experiments having meaningful bearing on the synthesis of camptothecin analogs are also described.

The extensive effort by many groups toward a total synthesis of the plant antitumor agent camptothecin (**1**) has recently culminated in four successful achievements.[3–6] The literature also contains a large number of studies directed toward a total synthesis[7–11] which show varying degrees of promise.

We describe our effort which led to the title compound **1** and is based upon initially obtaining deethyldeoxycamptothecin (**2**) which has already been readily converted to camptothecin by alkylation and hydroxylation of the active methylene group present in the molecule.[6] Construction of **2** was considered most efficient by linking two major units as designated by the dotted line. The precursor **3** was therefore highly desirable, since a cyclodehydration process of the aldehyde to the active methylene group (2 position of quinoline) should produce **2**. Formation of **3** was envisioned as being derived from the open-chain aldehyde **4** and the link-up to form the latter (dotted line) represented the key synthetic transformation in the total synthesis. The formation of **4** required that a Michael addition be performed using the unsaturated ester **5** and the hydroxy amide **6** (or in a masked form, *i.e.*, **7**). Since it is quite unreasonable to expect



1, R_1 = Et; R_2 = OH
2, $R_1 = R_2$ = H



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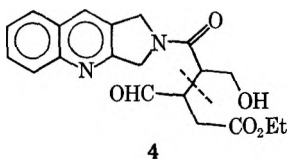

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(1) This study was supported by the National Institutes of Health.

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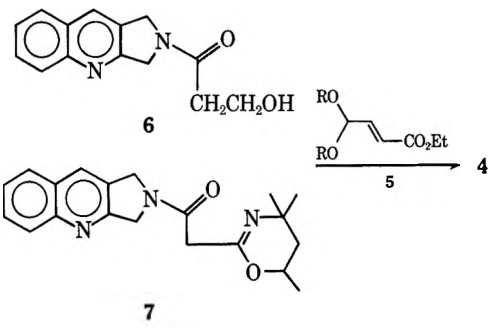
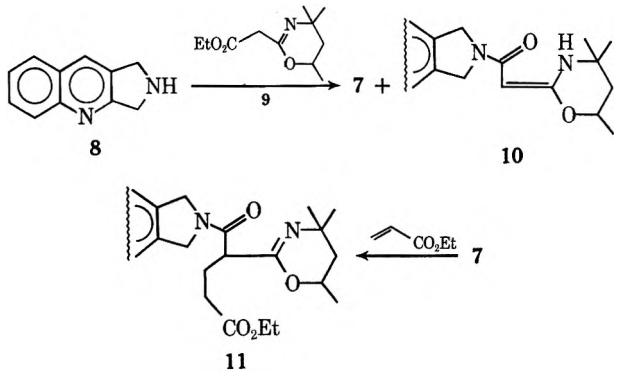
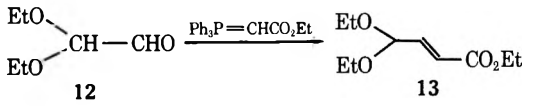


the hydroxy amide **6** to undergo a Michael addition at the α carbon to the amide group, the oxazine amide **7** was viewed as a plausible synthetic equivalent. The conversion of the oxazine ring to an aldehyde function and ultimately to a primary alcohol has already been demonstrated in previous synthetic efforts from this laboratory.[12] The preparation of **7** was accomplished in 85% yield by heating the readily available pyrrolo-[3,4-*b*]quinoline **8**[13] with the ester oxazine **9**[14] in the

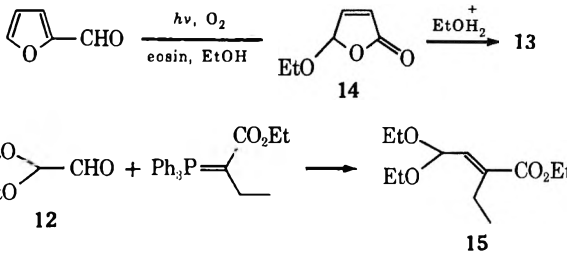


presence of DMF. The oxazine amide was obtained as the nonconjugated tautomer **7**, although exposure to base or heat converted it to an equilibrium mixture containing the exocyclic system **10**. A model experiment to ascertain the ability of **7** to undergo Michael addition with an α,β-unsaturated ester was proven successful when a solution of the oxazine amide and ethyl acrylate gave an 80% yield of the Michael adduct **11** after heating in ethanol overnight.

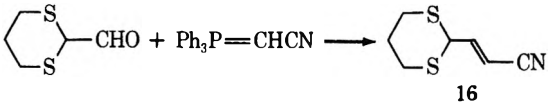
The second key moiety now necessary was the unsaturated ester containing a potential or masked aldehyde function **5**. The simplest system chosen was the diethyl acetal **13**, which was readily prepared by Wittig coupling of the known glyoxal diethyl acetal **12**.[15] Although the seemingly straightforward route gave **13** in pure trans form, the drawback to this method lay in the tedious procedure for obtaining **12** in workable



quantities. The best yield of **12** never exceeded 30% after various modifications for cleaving glyceraldehyde ethyl acetal[16] using lead tetraacetate or potassium permanganate (Experimental Section). The most convenient and efficient method for the preparation of **13** was found in the photooxidation[17] of furfural, which produced the lactone **14** in 56% yield. Hydrolysis of

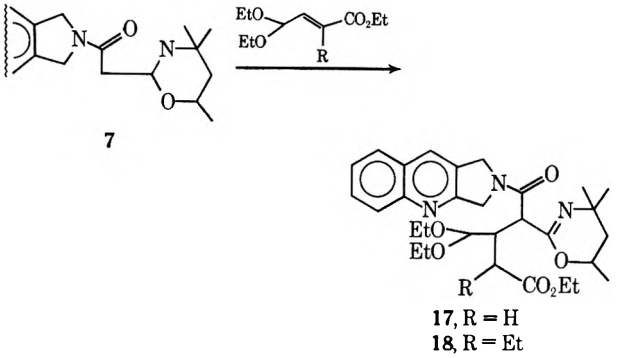


the latter in acidic ethanol led to the desired ester, **13**. In a concomitant effort to arrive at alternate precursors to **1**, the α-ethyl unsaturated ester **15** was also prepared by Wittig coupling to **12**. It was anticipated that the camptothecin precursor, if successfully reached, would then possess the requisite ethyl group, thus eliminating the need for introduction into the target molecule, **2**. An additional route to suitable electrophilic olefins analogous to **13** was devised[18] resulting in the dithiane derivative **16**. This system would also be



expected to serve as a Michael acceptor for **7** and both the nitrile and dithiane functions could be transformed into the needed ester and aldehyde, respectively.

With routes to three potential Michael acceptors in hand (**13**, **15**, and **16**) attention was turned to joining these to **7**, which, if successful, would afford the highly functionalized precursor **4**. After a series of experiments under varying conditions, the desired Michael adduct **17** was formed in 75% yield by heating **7** and **13**



in a sealed tube at 145° for 40 hr. Similar treatment of the ethyl-substituted acrylic ester **15** gave **18** but in only 22% yield. Owing to the poor yield of the latter product, coupled once again with the difficulty already mentioned for obtaining **12**, this approach was abandoned in favor of the readily accessible product **17**.

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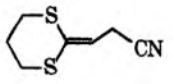
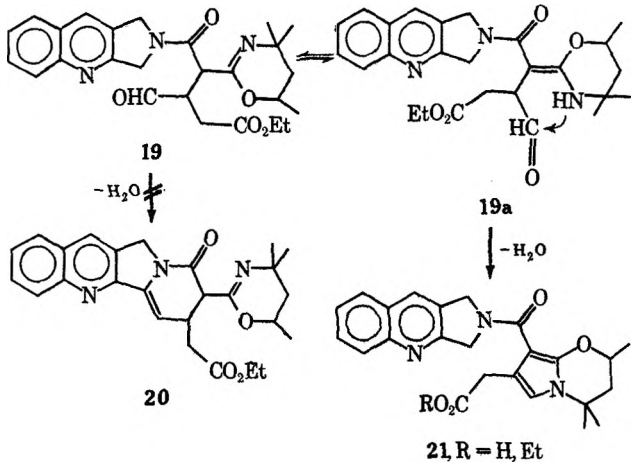
(18) A. I. Meyers and R. C. Strickland, *J. Org. Chem.*, **37**, 2579 (1972).

The Michael addition of **7** with the dithiane system **16** failed to produce any product other than recovered starting materials, which included the isomeric ethylene thioacetal **16a**. The facile isomerization of **16** to **16a** has already been discussed.[18]



16a

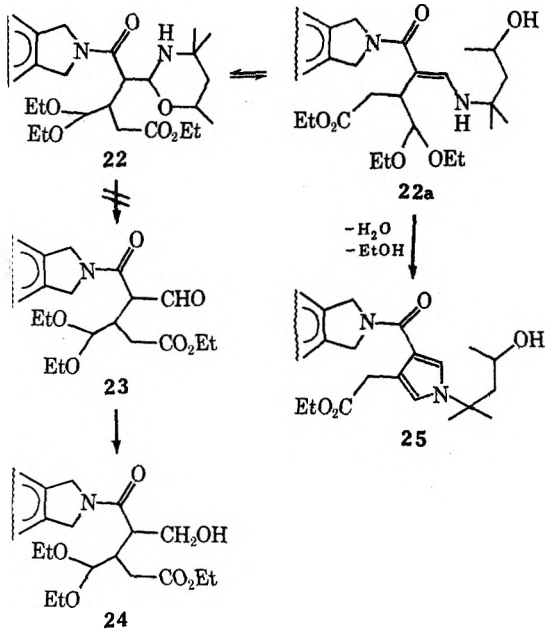
The next step in the synthesis obviously called for the release of the aldehyde from its ketal masking group in **17** followed by condensation of **19** to the



21, R = H, Et

dihydropyridone **20**. When this sequence was attempted under various acidic conditions, only the fused pyrrolooxazine **21** could be isolated. This product arises from the kinetically more favored cyclodehydration of the aldehyde function with tautomer **19a**. This pyrrole cyclization was found to be a general process and was recently demonstrated with a number of other examples.[19]

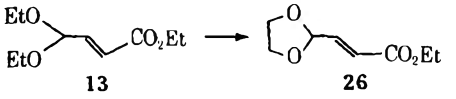
In an effort to circumvent this undesired reaction, the oxazine ring in **17** was reduced according to published procedures[14] to the tetrahydro derivative **22**.



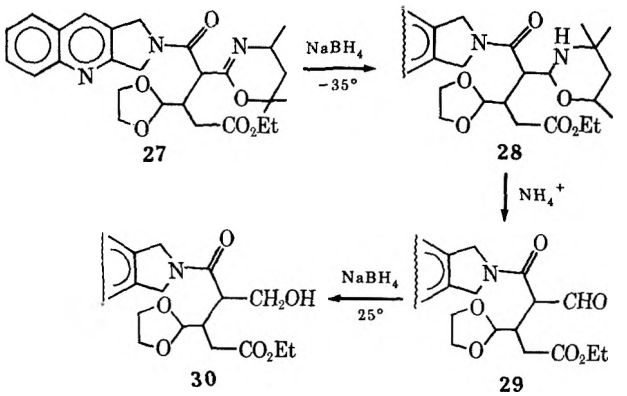
(19) A. I. Meyers, E. W. Collington, and T. A. Narwid, *J. Heterocycl. Chem.*, **8**, 875 (1971).

The goal at this point was to hydrolyze the tetrahydro-1,3-oxazine ring to the aldehyde **23** and *in situ* reduction to the carbinol **24** as performed in the earlier synthetic effort.[12] However, the only product obtained from hydrolytic experiments was the monocyclic pyrrole **25**, presumably derived from the open-chain tautomer **22a**.

The failure in selectively removing the tetrahydro-1,3-oxazine ring in **22** so that the aldehyde **23** could be prepared suggested that a more stable acetal was required which would remain intact during the conversion **22** → **23**. Since the 1,3-dioxolane masking group is more resistant to hydrolytic cleavage than acetals,[20] this modification was considered. Transacetalization of **13** to its dioxolane **26** was readily ac-



complished by treatment with ethylene glycol catalyzed by boron trifluoride etherate. Michael addition with **7** at 150° or in hot DMF gave the corresponding adduct **27** in good yield as a crystalline product. This is in

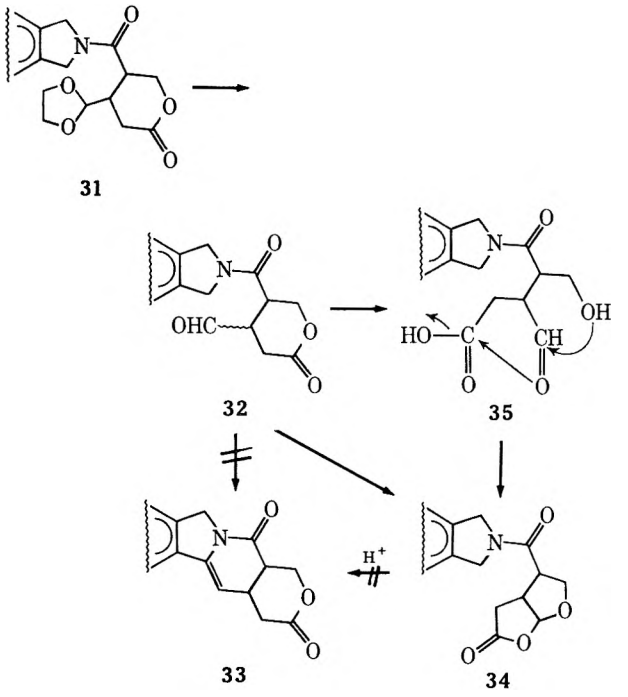


contrast to the adduct **17**, which was obtained as a foam and required purification *via* preparative layer chromatography. Reduction with aqueous sodium borohydride smoothly gave the tetrahydro-1,3-oxazine **28**. Mild hydrolysis using ammonium chloride (ethanol–water) led to the desired aldehyde, **29**, *with the dioxolane moiety remaining intact.* Routine reduction using sodium borohydride in ethanol resulted in the sought-after carbinol **30**, which now represented the synthetic equivalent of **4**.

The lactone **31** was readily prepared by heating the hydroxy ester **30** with sodium hydride in THF. It is of interest to note that alkaline saponification of **30** followed by neutralization did not spontaneously produce the lactone, which for camptothecin is known to form with great facility.[3-6] However, the lactone could be formed by treatment of the hydroxy acid with dicyclohexylcarbodiimide.

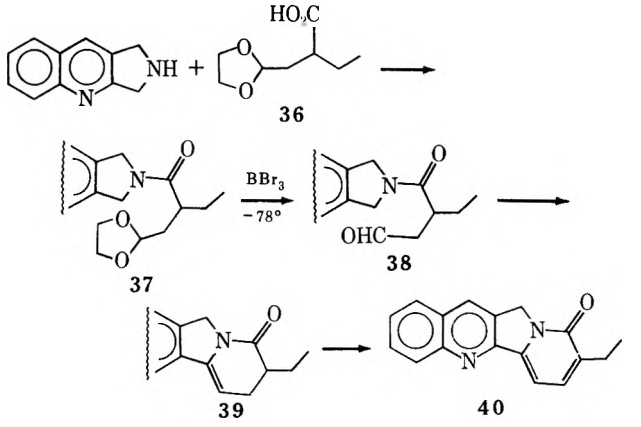
Attempts to release the aldehyde function to **32** followed by cyclodehydration to the pyridone **33** was once again frustrated by a facile rearrangement to the etiolactone **34**. A variety of Lewis acid catalysts were added to the dioxolane and in every case the formyl group preferred reaction with the lactone ring (or the hydroxy acid, **35**) rather than the pyrrolidine ring. The formation of the etiolactone may be considered some-

(20) J. F. W. McOmie, *Advan. Org. Chem.*, **3**, 248 (1963).



what analogous to the pyrrole formation described earlier (**19a** → **21**). Attempts were made to utilize **34** as a precursor to the pyridone **33**, since the former is, in effect, a "protected" aldehyde function which might exist in aqueous medium along with its open-chain equilibrium partner, **35**. Efforts in this direction proved fruitless owing to the stability of **34** under numerous aqueous acidic conditions.

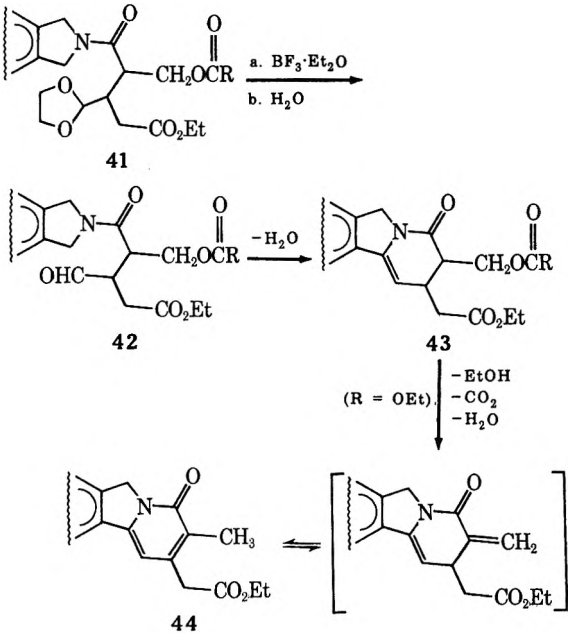
The failure to achieve a cyclodehydration of the aldehydes **32** and **19** (or **17**) to their respective dihydropyridones **33** and **20** prompted a study to ascertain whether this ring closure was indeed a feasible one. In this regard the dioxolane acid **36**[21] was chosen as a



suitable source for a model pyridone synthesis. Condensation with the pyrroloquinoline using dicyclohexylcarbodiimide gave the amide **37**, which surprisingly could not be transformed to the aldehyde **38** under a variety of aqueous acid conditions (1–3 *N* $HClO_4$, HCl, TsOH, TFA in THF, AcOH, EtOH solutions). The recovery of **37** in most cases was unexpected in view of the extensive literature[20] on dioxolane cleavages. The aldehyde was eventually obtained in 94% yield by adding boron tribromide to a dichloromethane solution of **37** at −78° followed by warming to room temperature.[22]

The aldehyde was cleanly cyclized (80%) to the dihydropyridone **39** using a catalytic quantity of trifluoroacetic acid in refluxing toluene. When the cyclization was carried out in benzene at 80°, only trace amounts of the pyridone could be detected using ultraviolet techniques (244 nm). The model study therefore reaffirmed the expectation that a pyridone may be formed efficiently from an aliphatic aldehyde. The addition of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to a benzene solution of **39** resulted in a quantitative conversion to the aromatized pyridone **40**.

Returning now to the hydroxy ester **30**, some modification was necessary to avert the etiolactone formation. The lactone **31** was unsuitable owing to its inability to remain intact during the removal of the dioxolane protecting group. The hydroxy ester was converted into its carbonate ester **41** (R = OEt) in the hope that this



moiety would be stable both to the dioxolane cleavage to **42** and the cyclodehydration to the pyridone **43**. Aqueous acid hydrolysis once again resulted in the etiolactone **34** and similar disappointing results were also obtained for corresponding acetate derivative **41** (R = Me). It was subsequently found that addition of the acetate or the carbonate ester **41** to excess boron trifluoride etherate at −78° followed by quenching this solution in cold water gave approximately 60% cleavage of the dioxolane to the aldehydes **42** (R = OEt and R = Me). The carbonate ester of **42** was treated with trifluoroacetic anhydride in refluxing toluene and the reaction was followed by ultraviolet spectroscopy. A pyridone was indeed formed but uv examination showed it to be aromatized. Further examination confirmed that the product from the cyclization of the carbonate aldehyde **42** was the methyl-substituted pyridone **44**. This material undoubtedly arose from expulsion of carbon dioxide and water from the carbonate, giving the exocyclic methylene tautomer of **44**. The acetate of **42** was next

(21) This was chosen since it was available from another study and possessed the necessary functionality to achieve our purpose.

(22) Although this technique worked exceedingly well in the case cited, an examination into its generality with various other dioxolanes proved disappointing.

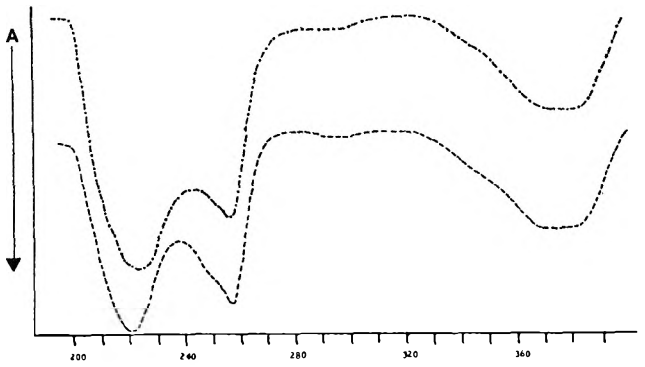
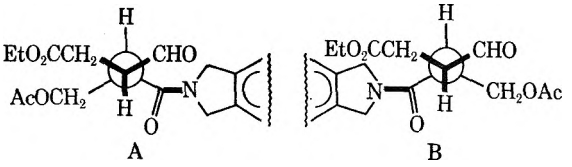


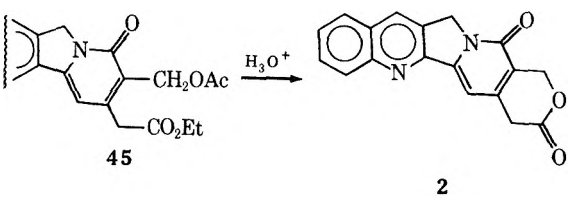
Figure 1.—Ultraviolet spectrum (95% ethanol) of deoxydeethylcamptothecin (-·-·-·) and camptothecin (------).

subjected to cyclization conditions using benzene as the solvent and trifluoroacetic acid or acetic anhydride as the catalyst. In this fashion the dihydropyridone **43** (R = Me) was obtained, which was aromatized to the pyridone **45** in 21% overall yield from the aldehyde **42**. The low yield of cyclization of the aldehyde **42** to the pyridone **43** (R = Me) was due to a mixture of two aldehyde diastereomers in **42**. Thus, when the dioxolane **41** was cleaved with boron trifluoride there were present in the product two aldehyde protons in the ratio 3:1. Owing to the low yield of cyclization, it was felt that one of these diastereomers was incapable of cyclizing because of an unfavorable conformation. Inspection of rotamer structures for **42** reveals that only A is conformationally equipped to cyclize to the



methylene group of the pyrroloquinoline, whereas the other diastereomer has B as its most stable conformer. This hypothesis was confirmed when the mixture of aldehydes **42** was heated in methanol containing silica gel and isomerization occurred to a new ratio (the lesser one originally present in the mixture became the predominant product). When the isomerized material was subjected to acid-catalyzed cyclodehydration in an attempt to prepare the dihydropyridone **43**, only a trace amount was detected; the remainder of the reaction mixture consisted of starting material. Thus, it may be concluded that only the major isomer, formed initially during the boron trifluoride cleavage, may serve as a useful precursor in the synthetic scheme and epimerization of B to A does not take place during the acidic cyclizing conditions.

With the desired dihydropyridone **43** in hand, aromatization to the pyridone **45** was readily achieved



by DDQ oxidation in benzene. The camptothecin precursor **2** was formed by treatment of the acetate ester with dilute sulfuric acid, causing hydrolysis of both ester functions and spontaneous closure of the lactone ring. Comparison of the ultraviolet spectrum of **2** with that of camptothecin (Figure 1) confirmed the pentacyclic lactone structure. The recent report by Winterfeldt[6] on the total synthesis of camptothecin describes the formation of **2**, although no physical data were given. Since the ethylation and hydroxylation of **2** has already been shown by Winterfeldt to lead to camptothecin, the preparation of this substance formally concluded the total synthesis. Nevertheless, **2** was treated as a suspension in dimethoxyethane (DME) with excess sodium hydride and afforded only moderate yields of the deoxycamptothecin **1** (R_1 = Et; R_2 = H). Also present in the product of this reaction was camptothecin, presumably formed by air oxidation of the anion of **1**. Hydroxylation of the tertiary carbon in **1** (R_1 = Et; R_2 = H) has already been noted by Danishefsky[4] to occur on standing in air. No further effort was expended or is planned in this direction in light of the results by Winterfeldt coupled with the recent clinical data[23] questioning the antitumor activity of camptothecin. It now appears that **2** may be a more valuable system for further study in that it may be alkylated with substituents other than ethyl in an attempt to find enhanced pharmacological activity.

In summary, this approach has been shown to produce the pentacyclic ring system of camptothecin and further effort could conceivably increase the overall efficiency of the synthesis. By far the most serious synthetic difficulty *via* this approach is the alkylation of **2**, which proceeds poorly, and this has been noted by other workers.[4,6,6a] Further studies should be directed toward alkylation of the ester **45**, whose solubility is far greater than that of the lactone **2** and would ultimately provide the α-alkylated lactone upon hydrolysis.

Experimental Section[24]

Pyrrol[3,4-*b*]quinoline (8).—This material was prepared according to the method previously described[13] and also received from the National Cancer Institute as a crude dihydrobromide salt. The unstable free base was liberated as follows. The salt (20 g) was added to 200 ml of dichloromethane in a separatory funnel and treated with 30 ml of 40% sodium hydroxide and 25 ml of water. After shaking for several minutes the salt dissolved and the organic layer separated. The aqueous solution was further extracted with dichloromethane and the combined extracts were dried (K_2CO_3) and concentrated, leaving 9.5 g of tan solid. Purification was achieved by sublimation (90–110°, 0.05 mm), mp 103–104.5°. The material darkens on standing in the atmosphere: ir (KBr) 3200, 1640, 1570 cm^{-1}; nmr ($CDCl_3$) δ 2.4 (NH), 4.4 (br s, 4), 7.3–8.2 (m, 5).

Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.59; H, 5.92; N, 16.60.

Oxazine Amide 7.—A mixture consisting of 11.2 g (66 mmol) of **8**, 17.1 g (80 mmol) of ester oxazine 9,[14] and 3.5 ml of dimethylformamide was placed in a flask equipped with a distillation

(23) Dr. Robert E. Engle of the National Cancer Institute, Bethesda, Md.

(24) All melting points and boiling points are uncorrected. Microanalyses were performed by Midwest Micro Labs, Indianapolis, Ind. Nmr spectra were taken on a Varian T-60 using tetramethylsilane as an internal standard. Mass spectra were taken on an AEI MS-9 at 70 eV. Ultraviolet and infrared spectra were taken on Perkin-Elmer 202 and 257 instruments, respectively. Preparative layer chromatography was performed using Merck AG, PF_{254} silica gel containing a fluorescent indicator, while column chromatography employed Merck AG, 0.05–0.2 mm silical gel. Thin layer chromatography utilized Eastman chromagram silica gel sheets.

head and lowered into an oil bath preheated to 145–150°. The temperature was raised to 165–170° and maintained for 3.5 hr, upon which the mixture solidified. After cooling, the crude product was recrystallized (ethanol), affording 18.3 g (83%): mp 174–180° (decomposition begins at 168°); ir (Nujol) 1680, 1655 cm^{-1}; nmr ($CDCl_3$) δ 1.2 (s, 6), 1.4 (s, 3), 1.6 (m, 2), 3.4 (s, 2), 4.3 (m, 1), 5.0 (br s, 4), 7.4–8.2 (m, 5); uv (EtOH) 212, 231 nm.

Anal. Calcd for $C_{20}H_{23}N_3O_2$: C, 71.19; H, 6.87; N, 12.45. Found: C, 70.94; H, 6.83; N, 12.44.

Michael Addition of 7 with Ethyl Acrylate 11.—A solution of the oxazine amide (189 mg, 0.56 mmol) and ethyl acrylate (52 mg, 0.56 mmol) in 2.5 ml of ethanol was heated to reflux for 20 hr. The solvent was removed and the viscous residue was recrystallized from ethanol to give 101 mg (80%) of 11: mp 156–157°; ir (Nujol) 1740, 1660, 1630 cm^{-1}.

Anal. Calcd for $C_{25}H_{31}N_3O_4$: C, 68.63; H, 7.14; N, 9.60. Found: C, 68.36; H, 7.06; N, 9.71.

Glyoxal Diethyl Acetal 12.—A solution of *dl*-glyceraldehyde diethyl acetal[16] (29.5 g, 0.18 mol) in dry benzene, under nitrogen, was cooled in an ice bath and treated with dry lead tetraacetate (85 g, 0.19 mol) in small portions from Gooch tubing. When the addition was complete, the suspension was stirred at 25° for 1 hr and filtered. The filtrate was treated with 40 g of anhydrous sodium carbonate in small portions while cooling. The suspension was filtered again and the filtrate was concentrated. The residue was taken up in ether, filtered, and evaporated to leave a colorless oil (21.5 g). The ir and nmr spectrum exhibited only a trace amount of carbonyl absorption and aldehyde proton (9.6 ppm), respectively. This product was a dimer or trimer of the desired product 12. Monomerization was achieved by heating 10-g samples under nitrogen at 270–290° (Wood's metal bath) and collecting the distillate in a Dry Ice–acetone trap. The distillate consisted of a mixture of solid and liquid material, which was separated by filtration, and the solid was washed with ether. The ether washings were combined with the filtrate and the mixture was distilled. The aldehyde boiled at 65° (55 mm), yielding 10.3 g (31%), and could be stored at −20° under nitrogen for 5 days without significant polymerization: ir (film) 1740 cm^{-1}; nmr (CCl_4) δ 1.3 (t, 6), 3.7 (d of q, 4), 4.5 (d, J = 2, 11 Hz, 1), 9.6 (d, J = 2 Hz, 1).

Ethyl 4,4-Diethoxy-2-butenoate (13).—The modified Wittig technique described by Bestmann[25] was employed. A suspension of methyltriphenylphosphonium iodide (6.15 g, 15 mmol) in dry benzene (40 ml) at 0°, under nitrogen, was treated dropwise with *n*-butyllithium (9.51 ml, 15% in hexane). The dark red mixture was stirred for 1 hr at 25° and a solution of ethyl chloroformate (0.82 g, 76 mmol) in 5 ml of benzene was added. After 30 min, a solution of glyoxal diethyl acetal 12 (1.0 g, 7.6 mmol) in 5 ml of benzene was added. The mixture was stirred for 16 hr at 25° and quenched in water. Extraction with ether, drying (K_2CO_3), and concentration produced a residue, which was taken up in pentane and filtered to remove triphenylphosphine oxide. The pentane solution, after concentration, provided an oil which gave upon distillation 0.92 g (60%) of 13: bp 65° (0.4 mm) [lit.[15] bp 70–73° (0.3 mm)]; ir (film) 1725 cm^{-1}; nmr (CCl_4) δ 1.2 (t, 6), 1.3 (t, 3), 3.6 (d of q, 4), 4.2 (q, 2), 5.0 (d of d, 1), 6.1 (d of m, J = 16 Hz, 1), 6.8 (d of d, J = 4, 16 Hz, 1).

Ethyl 2-Ethyl-4,4-diethoxy-2-butenoate (15).—The procedure was the same as described for 13. From *n*-propyl triphenylphosphonium bromide (2.93 g, 7.6 mmol), *n*-butyllithium (4.76 ml, 15% w/w in hexane), ethyl chloroformate (0.41 g, 3.8 mmol), and glyoxal diethyl acetal (0.5 g, 3.8 mmol), the α-ethyl unsaturated ester 15 was obtained as a colorless oil: bp 77–78° (0.4 mm); 0.67 g (76%); ir (film) 1730 cm^{-1}; nmr (CCl_4) δ 0.8–1.4 (three sets of overlapping triplets, 12), 2.3 (q, 2), 3.5 (d of q, 4), 4.2 (q, 2), 5.2 (d, J = 7 Hz, 1), 6.5 (d, J = 7 Hz, 1).

Preparation of 13 from Photooxidation of Furfural.—Freshly distilled furfural (50 g, 0.52 mol), 29 mg of eosin, and 229 mg of 2,4-di-*tert*-butyl-4-methylphenol dissolved in 430 ml of absolute ethanol were placed in a Pyrex photochemical reaction vessel fitted with an oxygen inlet (fritted disc) and reflux condenser. The entire reaction vessel was then surrounded by aluminum foil and the oxygen was bubbled through the solution at a rapid rate. The light source was turned on (Sylvania FBD 500W, 120 V) and kept cool by a rapid stream of air. Irradiation was carried out for 34 hr, when an additional 25 mg of eosin was introduced and irradiation was continued for 24 hr longer. The progress of the reaction was followed by vpc analysis (UCON-98, 10% on 80–100 Chromosorb W, 6-ft column). When inspection indicated that the reaction was >90% complete, the lamp was turned off and the ethanol was removed *in vacuo*. The residual amber oil was distilled, bp 71–72° (2.8 mm), to give 37 g (56%) of the lactone 14: ir (film)[17,26] 3100, 1795, 1760 cm^{-1}; nmr ($CDCl_3$) δ 1.4 (t, 3), 3.9 (d of q, 2), 6.0 (d, J = 0.5 Hz, 1), 6.3 (d, J = 6 Hz, 1), 7.4 (d, J = 6 Hz, 1).

Conversion of 14 to the unsaturated ester 13 was achieved by heating to reflux a solution containing 60 g (0.46 mol) of the lactone, 20 ml of boron trifluoride etherate, and 500 ml of absolute ethanol. Removal of samples at 30-min intervals revealed (vpc) that two olefins (cis and trans) were being formed with the cis isomer predominating at the early stages. After 4 hr of reflux, the mixture stabilized to a 4:1 ratio of trans to cis and the heating was terminated. A third, higher boiling component, was also present and was presumed, by cursory nmr examination, to be the Michael addition product of ethanol to the unsaturated ester 13. The ethanol solution was cautiously treated with anhydrous sodium bicarbonate and the solution was filtered and concentrated. The resulting oil was triturated with ether and filtered to a clear solution. After removal of the ether, distillation was carried out using a 12-in. Vigreux column affording 37 g (40%) of 13 from the fraction boiling at 72–82° (2 mm). The product consisted of a cis–trans mixture (80:20).

Preparation of Dioxolane Unsaturated Ester 26 from 13.—A solution containing 36.3 g (0.18 mol) of 13, 16.6 g (0.27 mol) of ethylene glycol, and 15 ml of boron trifluoride etherate was stirred at room temperature for 2–4 hr and then treated with 20 ml of water and solid sodium bicarbonate. Upon becoming neutral, the mixture was extracted three times with chloroform, dried (Na_2SO_4), and concentrated. Vpc examination of the residue revealed a small quantity of the diethoxy derivative 13 still present, so the crude product was subjected to 0.3 equiv of ethylene glycol and 5 ml of boron trifluoride etherate. After 2 hr, the reaction was worked up as above and the crude material was totally devoid of 13. Distillation (bp 83–88°, 2 mm) gave 17.0 g (58%) of the dioxolane derivative as a 10:1 mixture of trans and cis isomers: ir (film) 2990, 2890, 1720, 1660 cm^{-1}; nmr ($CDCl_3$) δ 1.3 (t, 3), 4.0 (s, 4), 4.3 (q, 2), 5.5 (d, 0.85 H, J = 4 Hz), 6.2 (m, 1.15 H, J = 4 Hz), 6.8 (d of d, 0.9 H, J = 4, 16 Hz).

Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.57; H, 7.12.

Michael Adduct 17.—A mixture consisting of 0.88 g of the diethoxy acetal 13, 1.1 g of the oxazine amide 7, 4.5 ml of absolute ethanol, and 5 drops of a sodium ethoxide solution (from 20 mg of sodium and 0.4 ml of ethanol) was heated in a sealed tube at 145–147° for 42 hr. Upon cooling in a Dry Ice–acetone bath, the tube was opened and the solution was concentrated *in vacuo*. The residue was dissolved in ether and, after standing for 1 hr, the precipitate of unreacted oxazine amide 7 was removed (0.09 g) and the filtrate was placed on five 20 × 40 cm plates coated to 1.5 mm with silica gel (Merck PF_{254}). The plates were eluted with acetone–benzene (1:1) and the desired band (R_f 0.76) was recovered with hot methanol. The total yield of 17 was 1.25 g (78%) as a foam: ir (film) 1735, 1675–1650 cm^{-1}; nmr ($CDCl_3$) δ 0.8–1.8 (m, 21), 2.6 (d of d, 2), 3.3 (m, 1), 3.6 (d of q, 4), 4.1 (m, q, 3), 4.6 (d, 1), 5.0 (s, 2), 5.2 (m, 2), 7.4–8.2 (m, 5); *m/e* 539.

Anal. Calcd for $C_{30}H_{41}N_3O_6$: C, 66.77; H, 7.66; N, 7.79. Found: C, 66.41; H, 7.84; N, 7.74.

Michael adduct 18 was prepared in the same manner as the adduct 17 by use of the α-ethyl unsaturated ester 15 and the oxazine amide 7. The crude product, after being placed on a preparative layer plate (1.5 mm, 20 × 40 cm) and eluted with benzene–acetone (3:2), gave a band (R_f 0.48) which was removed and washed with hot methanol. The residue was a pale yellow glass: ir (film) 1730, 1667, 1655 cm^{-1}; nmr ($CDCl_3$) δ 0.8–2.0 (m, 26), 2.8–3.2 (br m, 1), 3.6 (m, 5), 4.2 (q, m, 3), 4.6 (m, 1), 5.0 (s, 2), 5.3 (br s, 2), 7.4–8.2 (m, 5).

Anal. Calcd for $C_{32}H_{45}N_3O_6$: C, 67.74; H, 7.90; N, 7.14. Found: C, 67.70; H, 7.99; N, 7.40.

Pyrrolooxazine 21 (R = H).—The Michael adduct 17 (302 mg, 0.56 mmol) was added to 3.5 ml of 6% hydrochloric acid and the solution was stirred at room temperature for 21 hr. The precipitate which formed (120 mg) was collected on a filter. The

(25) H. J. Bestmann and H. Schulz, *Angew. Chem.*, **73**, 27 (1961).

(26) C. S. Foote, M. T. Wuesthoff, S. Wexler, I. G. Burstain, R. Denney, G. O. Schenk, and K. H. Schulte-Elte, *Tetrahedron*, **23**, 2583 (1967).

solid was added to water and the mixture was adjusted to pH 7 with sodium carbonate solution. The solution was extracted with dichloromethane, dried ($MgSO_4$), and concentrated, leaving a colorless, crystalline solid, 86 mg (37%). Recrystallization from ethanol gave pure material: mp 188–189° (carbon dioxide evolution followed by resolidification, mp 238–239°); ir (KBr) 3320, 3025, 2600, 1750, 1575, 1545 cm^{-1}; nmr ($CDCl_3$) δ 1.6 (s, d, 10), 2.0 (t, 2), 3.6 (s, 2), 4.6 (m, 1), 5.2 (br s, 4), 6.4 (s, 1), 7.6–8.3 (m, 5).

Anal. Calcd for $C_{24}H_{25}N_3O_4$: C, 68.72; H, 6.01; N, 10.02. Found: C, 68.45; H, 6.13; N, 10.09.

The product resulting from the decarboxylation of **21** (R = H) and melting at 238–239° was found to be the methyl derivative (RO_2CCH_2 in **21** = CH_3) by heating 50 mg of **21** on a hot stage at ~250°. Recrystallization of the crude material from ethanol, mp 238–239°, showed ir (film) 3020, 1620, 1540 cm^{-1}; nmr ($CDCl_3$) δ 1.5 (s, d, 10), 1.9 (d, 2), 2.1 (s, 3), 4.4 (m, 1), 5.1 (br s, 4), 6.1 (d, J = 2 Hz, 1), 7.5–8.1 (m, 5).

Anal. Calcd for $C_{23}H_{25}N_3O_2$: C, 73.58; H, 6.71; N, 11.19. Found: C, 73.49; H, 6.70; N, 11.20.

Pyrrolooxazine 21 (R = Et).—Heating a solution of **17** (220 mg, 0.41 mmol) in 5 ml of xylene containing 7 mg of *p*-toluenesulfonic acid and 2 ml of water for 18 hr gave, after evaporation of the solvent, a gummy solid. The latter was chromatographed on a preparative layer plate (1.5 mm) using benzene–acetone (2:1) as the eluent. The band with R_f 0.4 was cut from the plate and washed with hot methanol. After concentration, there was obtained 141 mg (78%) of the pyrrolooxazine: mp 88–89°; ir (film) 3010, 1735, 1620 cm^{-1}; nmr ($CDCl_3$) δ 1.2 (t, 3), 1.5 (m, 9), 2.0 (d, 2), 3.7 (s, 4), 4.1 (q, 2), 4.4 (m, 1), 5.2 (s, 4), 6.3 (s, 1), 7.4–8.2 (m, 5); *m/e* 447.

Anal. Calcd for $C_{26}H_{29}N_3O_4$: C, 69.78; H, 6.53; N, 9.39. Found: C, 68.85; H, 6.41; N, 8.82.

Reduction of Michael Adduct 17 to the Tetrahydro-1,3-oxazine 22.—A solution of the Michael adduct **17** (200 mg, 0.37 mmol) in 10 ml of tetrahydrofuran–ethanol (1:1) was cooled to −40° in a Dry Ice–acetone bath. A solution of sodium borohydride (4 mg, 0.37 mmol in 0.75 ml of water containing a drop of 20% sodium hydroxide) was added dropwise simultaneously with 10% hydrochloric acid solution such that the pH of the reaction remained at 5 and the temperature at −35 to −45°. After the addition was complete, the temperature was kept at −40° for 1 hr and the mixture was poured into 10 ml of water. The solution was rendered alkaline by the addition of 20% sodium hydroxide and then extracted with chloroform. The extracts were dried (Na_2SO_4) and evaporated, leaving 185 mg of crude **22**. Purification on preparative layer chromatography using acetone–benzene (1:1) as the eluent provided 120 mg (60%) of pure **22**: mp 37–40°; ir (film) 3220, 1740, 1660 cm^{-1}; *m/e* 541.

Anal. Calcd for $C_{30}H_{43}N_3O_6$: C, 66.52; H, 8.00. Found: C, 66.30; H, 7.76.

Pyrrote 25.—A solution of the tetrahydro-1,3-oxazine **22** (70 mg) in 20 ml of wet benzene containing 10 mg of *p*-toluenesulfonic acid was heated to reflux with a Dean–Stark trap for 18 hr. After cooling, the solution was evaporated and the residue was placed on a preparative layer plate. Elution with acetone–benzene (1:1) provided a band (R_f 0.28) which was cut from the plate and removed with methanol, giving 19 mg (32%) of a foam: ir (film) 3300, 1740, 1620 cm^{-1}; nmr ($CDCl_3$) δ 1.1 (d, 3), 1.2 (t, 3), 1.2 (br, OH), 1.6 (s, 3), 1.7 (s, 3), 1.9 (m, 2), 3.8 (m, 1), 3.7 (s, 2), 4.2 (q, 2), 5.2 (br s, 4), 6.9 (d, 1), 7.3 (d, 1), 7.5–8.1 (m, 5); *m/e* 449.

Michael Adduct 27. A. Sealed-Tube Reaction.—A mixture of 3.8 g (11.3 mmol) of the oxazine amide **7**, 2.9 g (17 mmol) of the dioxolane ester **26**, 17 ml of absolute ethanol, and 5–6 drops of sodium ethoxide solution was heated to 145–150° in a Pyrex tube which had been sealed under vacuum. Heating was continued for 8–10 hr and the solution was cooled, leaving a colorless precipitate under the amber-colored solution. Removal of the solid by filtration afforded 4.31 g (75%) of the Michael adduct: mp 202–203°; R_f 0.74 (acetone–benzene, 1:1) on Eastman chromagram silica gel; ir (KBr) 3050, 1737, 1660, 1645 cm^{-1}; nmr ($CDCl_3$) δ 1.2 (s, 6), 1.3 (d, t, 6), 1.6 (d of t, 2), 2.6 (m, 3), 3.3 (m, 1), 3.9 (m, 4), 4.2 (m, 3), 5.0–5.2 (s, m, 5), 7.5–8.2 (m, 5); *m/e* 509.

Anal. Calcd for $C_{28}H_{35}N_3O_6$: C, 65.99; H, 6.92; N, 8.51. Found: C, 65.72; H, 6.74; N, 8.46.

B. Heating in Dimethylformamide.—A solution containing 559 mg of **7** and 425 mg of **26** in 3 ml of dry DMF was heated to reflux for 30 hr. The reddish-brown solution was cooled, treated with 4 ml of ether, and stored at −20° overnight. The precipitate which formed was removed by filtration, 468 mg (51%), mp 201–202°. The spectral characteristics were identical with those of the product formed in the sealed-tube experiment.

Tetrahydro-1,3-oxazine 28.—The Michael adduct **27** (4.00 g, 7.9 mmol) was dissolved in 150 ml of hot ethanol and to this was added 150 ml of tetrahydrofuran. The solution was cooled, with magnetic stirring, to −45° by a Dry Ice–acetone bath. The pH was adjusted to 5 with 3 *N* hydrochloric acid and a solution of sodium borohydride (0.29 g in 0.5 ml of water containing a drop of 20% sodium hydroxide) was added dropwise. The pH was maintained at 5–6 by the simultaneous addition of 3 *N* HCl (monitored by pH paper). Stirring was continued after the hydride addition was complete at −40° and the solution was poured into 300 ml of cold water saturated with brine. The aqueous mixture was extracted with several portions of dichloromethane, and the extracts were dried ($MgSO_4$) and concentrated, leaving a foamy residue. The crude product was chromatographed on silica gel (0.05–0.2 mm, Merck AG-Darmstadt) through a 5 × 0.75 in. column using acetone–benzene (1:1) as the eluent. The desired product came off first and 3.5 g (87%) was obtained as a colorless foam: ir (film) 3450 (broad), 3330, 1730, 1640 cm^{-1}; nmr ($CDCl_3$) δ 0.9–1.6 (m, 14), 2.6 (m, 4), 3.4 (m, 1), 3.9 (m, 5), 4.2 (q, 2), 4.8 (d, 1), 5.0 (s, 2), 5.2 (m, 3), 7.5–8.2 (m, 5); *m/e* 511.

Anal. Calcd for $C_{28}H_{37}N_3O_6$: C, 65.81; H, 7.11; N, 8.23. Found: C, 65.71; H, 7.39; N, 7.99.

Ester Aldehyde 29.—To 35 ml of a gently refluxing ammonium chloride solution (25%) was added, dropwise, 1.38 g (2.7 mmol) of the tetrahydro-1,3-oxazine **28** dissolved in 9 ml of ethanol. The solution was heated for an additional 45 min and then cooled and treated with 50 ml of saturated brine solution. The contents were then extracted with chloroform (3 × 15 ml) and the extracts were dried ($MgSO_4$) and concentrated. The residue, a tan-colored foam, was chromatographed on silica gel eluting with acetone–benzene (1:1). Thin layer examination indicated that the aldehyde (R_f 0.63 on Eastman chromagram sheets) was free of impurities. The product, a colorless foam, weighed 800 mg (72%): ir (film) 3420 (broad), 3060, 2760, 1735, 1725, 1640 cm^{-1}; nmr ($CDCl_3$) δ 1.2 (two overlapping triplets, 3), 2.6 (t, 2), 3.4 (m, 2), 3.9 (m, 4), 4.1 (q, 2), 4.9 (s, 2), 5.2 (m, 3), 7.5–8.1 (m, 5), 9.6 (d, 0.5 H), 9.7 (d of d, 0.5 H) (the spectral data are consistent with some enolic character for the aldehyde); *m/e* 412.

Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79. Found: C, 63.79; H, 6.02; N, 6.78.

Hydroxy Ester 30.—To 3.56 g (8.1 mmol) of the above aldehyde **29** in 30 ml of ethanol previously cooled to 0° was added 0.31 g of sodium borohydride. The cold solution was stirred for 10 min, made acidic (pH ~4) with 3 *N* hydrochloric acid, and then saturated with sodium chloride. Extraction with chloroform (3 × 50 ml) followed and the extracts were dried (Na_2SO_4) and concentrated to provide an orange foam, 3.33 g. The product was purified by elution with acetone–benzene (1:1) through a 12 × 1 in. column packed with silica gel (Merck AG, 0.05–0.2 mm). Thin layer examination revealed that the hydroxy ester (R_f 0.53, Eastman chromagram) was pure and was obtained as a solid: mp 134–136°; 1.7 g (52%); ir (KBr) 3400 (br), 1730, 1625, 1580 cm^{-1}; nmr ($CDCl_3$) δ 1.4 (t, 3), 2.8 (s, m, 3), 3.5 (m, 1), 3.8–4.5 (m, q, 9), 5.0 (s, 2), 5.1–5.4 (m, 3), 7.5–8.2 (m, 5); *m/e* 414.

Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.54; H, 6.59; N, 6.71.

Lactone 31.—A mixture of 601 mg of the hydroxy ester **30** in 14 ml of 1 *N* sodium hydroxide was heated to reflux for 75 min. After cooling, the solution was acidified to pH 4 with dilute hydrochloric acid and extracted with dichloromethane (8 × 20 ml). The extracts were dried ($MgSO_4$) and concentrated, affording the hydroxy acid as a colorless foam (429 mg, 82%): ir (KBr) 3200–3500, 1710, 1625 cm^{-1}; *m/e* 368 (386 − 18). Without further purification the hydroxy acid (636 mg) was treated with 340 mg of dicyclohexylcarbodiimide in 25 ml of tetrahydrofuran and stirred at room temperature for 18 hr. The solid which appeared was triturated with a small quantity of chloroform to separate the lactone from the insoluble dicyclohexylurea. After several repetitive chloroform treatments, the chloroform was concentrated to give 353 mg (58%) of **31**: mp 185–190°; *m/e* 368; ir (KBr) 1730, 1635 cm^{-1}. The lactone was insufficiently soluble in chloroform to obtain a clean nmr spectrum; however, a spectrum in trideuterioacetonitrile was taken, δ 2.8

(m, 3), 3.4 (m, 1), 3.8 (br s, 4), 4.6 (t, 2), 4.6–5.0 (m, 5), 7.5–8.2 (m, 5).

The lactone was also prepared by treating the hydroxy ester **30** in dimethylformamide with 1.0 equiv of sodium hydride and stirring at 25° for 4 hr. Quenching in water, followed by extraction with dichloromethane, gave the lactone after evaporation of the solvent.

Etiolactone 34 from Lactone 31.—A solution of **31** (300 mg) in wet toluene containing 0.2 equiv of *p*-toluenesulfonic acid (or trifluoroacetic acid) was heated to reflux in the presence of a Dean–Stark trap for 3 hr. Neutralization with solid sodium bicarbonate followed by *in vacuo* removal of the solvent left 157 mg of a colorless solid: mp 215–222° dec; *m/e* 324; ir (KBr) 1775, 1640 cm^{-1}; nmr ($CDCl_3$) δ 2.8 (d of d, 2), 3.2 (m, 1), 3.6 (d of d, 1), 4.4 (t of d, 2), 5.0 (br s, 4), 6.2 (d, J = 6 Hz, 1), 7.5–8.1 (m, 5); R_f 0.61 (benzene–acetone, 1:1, Eastman chromagram sheets). The etiolactone **34** was also formed when the hydroxy ester **30** was treated with 5% perchloric acid in tetrahydrofuran (1:1) and stirred for 16 hr at room temperature.

Dioxolane Amide 37.—The pyrroloquinoline **8** (2.23 g, 13.1 mmol) and the dioxolane carboxylic acid **36** (2.26 g, 13.1 mmol) were dissolved in 40 ml of dichloromethane and treated with 2.9 g (14 mmol) of dicyclohexylcarbodiimide in dichloromethane in a dropwise fashion. The reaction was mildly exothermic. The mixture was stirred at room temperature for 24 hr, after which the dicyclohexylurea was removed by filtration. The filtrate was concentrated and the mixture of oil and solid residue was triturated with ether. The solid was collected on a filter, 2.2 g (50%), and recrystallized from ethanol–ether: mp 137–138.5°; ir (KBr) 1635 cm^{-1}; nmr ($CDCl_3$) δ 1.0 (t, 3), 1.8 (m, 2), 2.3 (d of t, 1), 2.8 (m, 2), 3.9 (q, 4), 5.0 (m, 5), 7.5–8.2 (m, 5).

Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 70.17; H, 6.58; N, 8.72.

Aldehyde Amide 38.—A solution of the dioxolane amide **37** (835 mg, 2.56 mmol) in 40 ml of dichloromethane was cooled to −78° (Dry Ice–2-propanol) and treated with 1.8 ml of boron tribromide at a rapid rate of addition. A precipitate formed immediately and agitation was continued for 2 hr at −78°. The cold bath was removed and the solution was allowed to reach room temperature, wherein the precipitate had mostly dissolved. Saturated sodium bicarbonate (25 ml) was added until the pH reached 7–7.5. The organic layer was removed and the aqueous layer was extracted with dichloromethane. The extracts were combined, dried (Na_2SO_4), and passed through Norit to remove the deep amber coloration. Evaporation of the solvent left a gummy material, 675 mg (93%). Purification was achieved by elution through neutral alumina with dichloromethane: ir (film) 2700, 1730, 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.0 (t, 3), 1.6 (m, 2), 2.4–3.4 (m, 3), 5.0 (br s, 2), 5.2 (q, 2), 7.5–8.2 (m, 5), 10.0 (s, 1). The aldehyde was used without further purification for the next step.

Dihydropyridone 39.—To the aldehyde **38** (612 mg, 2.17 mmol) in 25 ml of freshly distilled toluene was added 10–15 mg of trifluoroacetic acid and the solution was heated, under nitrogen, to reflux in the presence of a Dean–Stark trap for 4 hr. The cooled reaction mixture was diluted with 25 ml of ether and the solution was washed with 10 ml of saturated sodium bicarbonate solution. The organic layer was dried (K_2CO_3) and concentrated, leaving 558 mg of a crude solid. The entire product was chromatographed on silica gel (0.05–0.2 mm, Merck AG) using ethanol–dichloromethane (1:50) as the eluent. There was obtained 456 mg (80%) of a light green, crystalline solid, mp 150–154°. The analytical sample was crystallized from ethanol: mp 152–156°; ir (KBr) 1660 cm^{-1}; uv (EtOH) 360, 295, 244 nm;[27] nmr ($CDCl_3$) δ 1.1 (t, 3), 1.8 (m, 2), 2.6 (m, 3), 5.0 (s, 2), 6.2 (d, t, 1), 7.5–8.2 (m, 5).

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.29; H, 6.40; N, 10.58.

Pyridone 40.—A solution of the dihydropyridone **39** (100 mg) in benzene (3 ml) was treated with 1.1 equiv (90 mg) of 2,3-dichloro-5,6-dicyanoquinone. A precipitate formed almost immediately and the mixture was stirred at room temperature for 2.5 hr. After removal of the solid material, which was washed with ether, the combined filtrates were concentrated to a small volume and added to a silica gel column. Elution with ethanol–chloroform (1:3) gave 97 mg (96%) of a crystalline product. Recrystallization from ethanol gave 70 mg of pyridone: mp 261–262° dec; ir (KBr) 1670, 1650, 1600 cm^{-1}; uv (EtOH) 365, 286, 253, 246, 218 nm; nmr ($CDCl_3$) δ 1.3 (t, 3), 2.8 (q, 2), 5.2 (s, 2), 7.3–8.4 (m, 7, the AB pattern of the pyridone protons is mixed with the multiplet of aromatic protons and is, therefore, not readily sorted out); *m/e* 262.

Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 78.06; H, 5.21; N, 10.86.

Carbonate Dioxolane 41 (R = OEt).—Ethyl chloroformate (20 mg) was added dropwise to a previously cooled (0°) solution of the hydroxy ester **30** (80 mg, 0.2 mmol) in 4 ml of pyridine. The resulting solution, after stirring for 16 hr at room temperature, was poured into cold 0.5 *N* hydrochloric acid and extracted with dichloromethane (3 × 10 ml). After the extract was washed with dilute sodium bicarbonate solution, it was dried ($MgSO_4$) and concentrated, leaving a tan-colored foam, 82 mg (87%). The carbonate was purified by preparative layer chromatography (R_f 0.71) using acetone–benzene (1:1): ir (film) 1755–1740 (br), 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.3 (t, 6), 2.7 (m, s, 3), 3.4 (m, 1), 3.9 (br s, 4), 4.2 (q, 4), 4.5 (t, 2), 5.0 (s, m, 5), 7.5–8.2 (m, 5); *m/e* 486.

Acetate Dioxolane 41 (R = CH_3).—A solution of the hydroxy ester **30** (130 mg, 0.31 mmol) in 2 ml of pyridine previously cooled to 0° was treated with 30 mg of acetyl chloride. The solution was stirred at 0° for 1 hr and then 2 hr at room temperature. The resulting mixture was poured into cold dilute 1 *N* hydrochloric acid and the aqueous solution was extracted with dichloromethane. The combined extracts were washed with aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated to give a tan oil (128 mg, 90%), R_f 0.70 (acetone–benzene, 1:1). The product could be, if desired, eluted through a silica gel column. However, this was found to be unnecessary, as the material was of sufficient purity to proceed further: ir (film) 1730–1740, 1670, 1645 cm^{-1}; nmr ($CDCl_3$) δ 1.3 (t, 3), 2.0 (s, 3), 2.7 (m, s, 3), 3.5 (m, 1), 4.0 (br s, 4), 4.2 (q, 2), 4.5 (d, 2), 5.0 (s, 2), 5.2 (m, 3), 7.5–8.3 (m, 5).

Acetate Aldehyde 42 (R = CH_3).—To a solution of 1.18 g (2.58 mmol) of the acetate dioxolane **41** (R = CH_3) obtained above, in 80 ml of dichloromethane cooled to −78° under argon, was added 6.5 ml (20 equiv) of boron trifluoride etherate. The cold bath was removed and the reaction mixture was allowed to warm to ambient temperature, at which time 20 ml of water was introduced and the mixture was stirred for 30 min. Partial neutralization to pH ~4 with 10% sodium hydroxide followed and the organic phase was separated, dried (Na_2SO_4), and concentrated. The residue (992 mg) was again dissolved in dichloromethane and treated with 2.7 ml (10 equiv) of boron trifluoride under the conditions described previously. Isolation, exactly in the same manner as above, was accomplished, producing 950 mg (94% based upon total yield of aldehyde) of a foam, R_f 0.87 (acetone–benzene, 1:1). The product, however, was a mixture containing ~30% of unidentifiable material and 70% of two diastereomeric aldehydes (**42**, R = CH_3). Owing to the similarity in tlc behavior, this mixture could not be separated and was used as such in the subsequent step: ir (film) 2720, 1745–1725 (br), 1645 cm^{-1}; nmr ($CDCl_3$) δ 1.3 (two triplets in the ratio of 7:3, 3), 2.0 (s, 3), 2.6–4.6 (m, 10, these signals contained two additional protons which are attributed to the impurity mentioned above), 5.0 (s, 2), 5.2 (m, 2), 7.5–8.3 (m, 5). Since the last two signals integrated perfectly with those at 2.0 and 1.3 ppm, the impurity does not appear to contain the pyrroloquinoline moiety nor the ethoxy or acetate groupings. Thus, it may be concluded that some rupture of the amide bond occurred during the dioxolane cleavage with boron trifluoride. Also present in the nmr spectrum of **42** are two aldehyde signals at δ 9.7 and 10.0 in the ratio 1:3, respectively.

Carbonate Aldehyde 42 (R = OEt).—The carbonate **41** (R = OEt) (300 mg, 0.7 mmol) was treated under the same conditions as the acetate **41** (R = CH_3) with boron trifluoride etherate, initially with 20 equiv and finally with 10 equiv, giving 237 mg of the crude corresponding aldehyde **42**. The product (81%) was also a mixture of two diastereomeric aldehydes and a substance derived from loss of the pyrroloquinoline moiety: ir (film) 2720, 1755–1730, 1648 cm^{-1}; nmr ($CDCl_3$) δ 1.2–1.4 (overlapping triplets, 6), 2.8–4.6 (m, 10), 5.0 (s, 2), 5.2 (m, 2), 7.5–8.3 (m, 5), 9.65 and 9.97 (total integration, 0.84 H) in the ratio of 1:3, respectively. The aldehyde mixture could not be separated from the impurity (~20%) and was used as such for the next step.

(27) J. A. Kepler, M. C. Wani, J. N. McNaull, M. E. Wall, and S. G. Levine, *J. Org. Chem.*, **34**, 3853 (1969).

Methylpyridone 44.—Trifluoroacetic anhydride (14 mg), toluene (4 ml), and the above carbonate aldehyde (**42**, R = OEt, 30 mg) were heated to reflux for 18 hr. The solution took on an immediate red color and, after the heating period, became very dark. The solution was diluted with 20 ml of chloroform and then washed with saturated sodium bicarbonate solution. Drying (Na_2SO_4) and concentration left a dark semisolid, 10 mg of which was subjected to preparative layer chromatography (silica gel, benzene–acetone, 1:1). A pure product, 2 mg, was cut from the plate: mp 258–261° dec; *m/e* 334; ir (film) 1730, 1650, 1600 cm^{-1}; uv (EtOH) 220, 253, 365 nm; nmr ($CDCl_3$) δ 1.3 (t, 3), 2.4 (s, 3), 3.7 (s, 2), 4.3 (q, 2), 5.2 (s, 2), 7.3 (s, 1), 7.6–8.5 (m, 5).

Dihydropyridone 43 (R = CH_3).—The acetate aldehyde (**42**, R = CH_3), as already described, was used as the diastereomeric mixture. A solution containing 500 mg (only 45% of which contained the usable precursor) of aldehyde mixture, 0.14 ml of acetic anhydride, and 50 ml of anhydrous benzene was heated to reflux for 24 hr. The cooled solution was treated with 10 ml of water and stirred at room temperature for 1 hr followed by neutralization with sodium bicarbonate. The benzene layer was separated, dried (Na_2SO_4), and concentrated, leaving a brown oily residue (375 mg). Although the product could not be purified (column or preparative layer chromatography), the ultraviolet spectrum indicated the presence of a dihydropyridone group (244, 295, and 360 nm), which compared favorably with the spectrum of **39**. The infrared and nmr spectrum indicated, among other products, the uncyclized aldehyde (δ 9.65). The crude dihydropyridone was then subjected without further rectification to the aromatization step which follows.

Pyridone 45.—The crude mixture from above (375 mg) was dissolved in anhydrous benzene (20 ml) and treated dropwise with 227 mg of 2,3-dichloro-5,6-dicyanoquinone (DDQ) as a solution in benzene. There was an immediate formation of a precipitate and the reaction was stirred at room temperature for 18 hr. The amber-colored solution was removed by filtration and the solid was washed with 15 ml of benzene. The combined filtrates were concentrated to a dark brown oil which was chromatographed on a silica gel column using ethanol–chloroform (3:1) as the eluent. The pyridone rapidly passed down the column and was followed by tlc, which showed an intense blue fluorescence upon exposure to an ultraviolet lamp. Evaporation of the solvents followed by addition of cold ethanol to the residue produced 48 mg (22% based upon the aldehyde **42**) of a solid. Recrystallization from hot ethanol gave 38 mg of pure pyridone: mp 242–244° dec; R_f 0.87 (acetone–benzene); *m/e* 392; ir (KBr) 1740, 1650, 1600 cm^{-1}; uv (EtOH) 220, 254, 361, 383 nm; nmr ($CDCl_3$) δ 1.3 (t, 3), 2.1 (s, 2), 4.8 (s, 2), 4.2 (q, 4), 5.3 (s, 2), 5.4 (s, 2), 7.3 (s, 1), 7.7–8.5 (m, 5).

Pentacyclic Lactone 2 (R_1, R_2 = H).—A mixture containing 24 mg of the pyridone ester **45**, 4 ml of ethanol, and 3 ml of 10% sulfuric acid was heated to reflux on a steam bath for 30 hr. Upon cooling the ethanolic solution, yellow crystals appeared: 17 mg (94%); mp 256–259° dec; *m/e* 304; ir (KBr) 1745, 1660, 1605 cm^{-1}; nmr (trifluoroacetic acid) δ 4.2 (s, 2), 5.8 (s, 2), 5.9 (s, 2), 8.0–9.5 (m, 6); for uv (EtOH) see Figure 1.

(±)-Deoxycamptothecin 1 (R_2 = H) and Camptothecin 1.—A suspension of 7 mg of **2** in 3 ml of 1,2-dimethoxyethane or dimethylformamide was treated with 1.0 mg of sodium hydride and the mixture was heated for 1.5 hr at 60°. Upon cooling to 0°, 1.5 mg of ethyl iodide was added and the mixture was slowly allowed to warm to ambient temperature and then stirred overnight. After quenching in water, the solid was collected and dried *in vacuo*. The infrared spectrum (KBr) exhibited bands at 1743, 1660, and 1600 cm^{-1}, identical with those of an authentic sample[28] of deoxycamptothecin 1 (R_2 = H). The mass spectrum exhibited a parent ion at *m/e* 332. An aged sample of the latter (2–4 days) in dichloromethane was examined by mass spectroscopy and found to give a molecular ion at *m/e* 348 as noted by Danishefsky.[4] In view of the reports by Winterfeldt[6] and Danishefsky[4] of the successful conversion of deoxycamptothecin to camptothecin coupled with the limited quantities on hand, no further effect was expended to prepare large quantities of **1**.

Registry No.—**1**, 7689-03-4; **2**, 38390-42-0; **7**, 39013-35-9; **8**, 34086-64-1; **8** (2HBr), 34086-65-2; **9**, 36867-19-3; **11**, 39013-39-3; **12**, 5344-23-0; **13**, 2960-65-8; **14**, 2833-30-9; **15**, 39010-34-9; **17**, 39013-42-8; **18**, 39013-43-9; **21** (R = H), 39013-44-0; **21** (RO_2CCH_2 = Me), 39013-45-1; **21** (R = Et), 39013-46-2; **22**, 39013-47-3; **25**, 39013-48-4; *cis*-**26**, 39013-49-5; *trans*-**26**, 39013-50-8; **27**, 39013-51-9; **28**, 39013-52-0; **29**, 39013-53-1; **30**, 39013-54-2; **31**, 39013-55-3; **34**, 39007-99-3; **36**, 39008-00-9; **37**, 39008-01-10; **38**, 39008-02-1; **39**, 39008-03-2; **40**, 39008-04-3; **41** (R = OEt), 39008-05-4; **41** (R = CH_3), 39062-22-1; *R*,S**-**42** (R = CH_3), 39010-34-9; *R*,R**-**42** (R = CH_3), 39010-35-0; *R*,S**-**42** (R = OEt), 39010-36-1; *R*,R**-**42** (R = OEt), 39010-37-2; **43**, 39062-20-9; **44**, 39008-06-5; **45**, 39008-07-6; ethyl acrylate, 140-88-5; *dl*-glyceraldehyde diethyl acetal, 10487-05-5; furfural, 98-01-1; hydroxy acid of **30**, 39008-08-7.

Acknowledgment.—The authors are grateful to Mr. James Sphon for the mass spectral data and to Mr. Daniel Yansura and Drs. Robert Gault, G. Ray Malone, and Elizabeth M. Smith for technical assistance.

(28) We wish to thank Professor S. Danishefsky for a sample of deoxycamptothecin for comparison purposes.

Nuclear Magnetic Resonance Spectroscopy. Application of Pulse and Fourier Transform Carbon-13 Nuclear Magnetic Resonance Techniques to Structure Elucidation. Rauwolfia Alkaloids[1]

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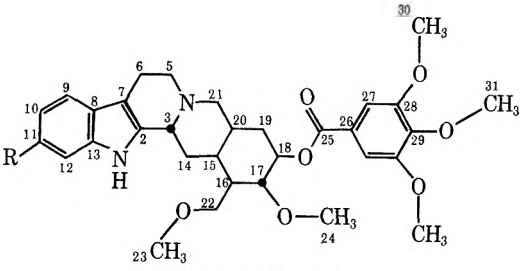
The natural-abundance pulse and Fourier transform ^{13}C nmr spectra of several Rauwolfia alkaloids have been recorded. Using noise-decoupling, partial single-frequency off-resonance decoupling (SFOR), and lanthanide chelate induced chemical-shift changes (lanthanide shifts), a self-consistent series of assignments have been made for the observed resonances.

We have previously commented on both the vast amount of research which has already been directed toward alkaloid structure elucidation and the possible application of ^{13}C magnetic resonance (^{13}C nmr) spectroscopy to this problem.[4] Our efforts in this area have been continuing and we would now like to report that with the aid of several advances in magnetic resonance techniques, which have been brought to fruition in the last few years, we are now able to record and interpret routinely, with a rather high degree of certainty, the ^{13}C nmr spectra of even rather complex alkaloids.

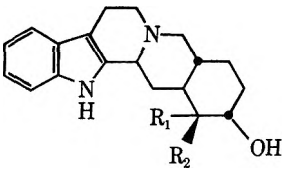
The natural-abundance ^{13}C magnetic resonance spectra of reserpine (I), deserpidine (II), corynanthine



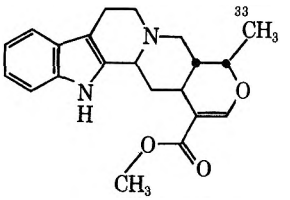
I, R = OCH_3(32)
II, R = H

(III), yohimbine (IV), ajmalicine (V), and reserpinine (VI) have been obtained using pulse and Fourier transform (PFT) techniques.[5] These alkaloids belong to the Rauwolfia family, with compounds I–IV belonging to the yohimbine group, and V and VI to the heteroyohimbine class.

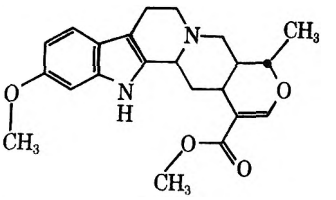
In the majority of instances, the observed resonances could be assigned to specific carbon atoms on the basis of noise-decoupling,[6-8] single-frequency off-resonance



III, R_1 = H; R_2 = CO_2CH_3
IV, R_1 = CO_2CH_3; R_2 = H



V



VI

decoupling (SFOR),[9,10] and lanthanide chelate induced chemical-shift changes.[11] Chemical modification of the various alkaloids was, in general, not required, thereby permitting total spectral analysis to be accomplished within a matter of hours. However, formation of simple derivatives such as methyl reserpate from reserpine was found to provide additional information on specific questions of spectral assignments.

A typical, completely proton-decoupled spectrum, that of reserpine, is shown in Figure 1. That the intensities of the peaks in this spectrum do not correspond in a simple way to the statistical numbers of carbons present is a consequence of unequal relaxation times and a short acquisition time for the free-induction decay signal.[5,12] Indeed, the acquisition time was purposely chosen to be sufficiently short so as to result in complete saturation of the signal of the deuteriochloroform used as solvent. This mode of operation is helpful in keeping the solvent peaks from overlapping the alkaloid peaks.

The collected data along with the corresponding assignments for alkaloids I–VI are presented in Tables I–III. Utilization of this data in alkaloid structure elucidation is relatively straightforward. As tabulations of carbon chemical shifts begin to appear with

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(2) National Institutes of Health Postdoctoral Fellow, 1971–1972.

(3) NATO Postdoctoral Fellow, 1970–1971.

(4) (a) W. O. Crain, Jr., W. C. Wildman, and J. D. Roberts, *J. Amer. Chem. Soc.*, **93**, 990 (1971); (b) P. W. Sprague, D. Doddrell, and J. D. Roberts, *Tetrahedron*, **27**, 4857 (1971); (c) see G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York, N. Y., 1972, Chapter 8, for references and discussion of procedures; (d) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, N. Y., 1972, also offers an excellent treatment of resonance assignments.

(5) T. C. Farrar and E. D. Becker, "Pulse and Fourier Transform NMR," Academic Press, New York, N. Y., 1971.

(6) F. J. Weigert, M. Jautelat, and J. D. Roberts, *Proc. Nat. Acad. Sci. U. S.*, **60**, 1152 (1968).

(7) L. F. Johnson and M. E. Tate, *Can. J. Chem.*, **47**, 63 (1969).

(8) R. R. Ernst, *J. Chem. Phys.*, **45**, 3845 (1966).

(9) H. J. Reich, M. Jautelat, M. T. Messe, F. J. Weigert, and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 7445 (1969).

(10) M. Jautelat, J. B. Grutzner, and J. D. Roberts, *Proc. Nat. Acad. Sci. U. S.*, **65**, 288 (1970).

(11) W. D. Horrocks, Jr., and J. P. Sipe, III, *J. Amer. Chem. Soc.*, **93**, 6800 (1971), and references cited therein.

(12) *Cf.*, for example, J. S. Waugh, *J. Mol. Spectrosc.*, **35**, 298 (1970); R. Freeman, K. E. R. Pachler, and G. N. LaMar, *J. Chem. Phys.*, **55**, 4586 (1971).

TABLE I

CARBON-13 CHEMICAL SHIFTS OF RAUWOLFIA ALKALOIDS[a]

Carbon	I	II	III	IV	V	VI	VII
2	61.9	61.8	58.4	58.0	58.1	59.7	58.3
3	131.8	133.0	132.2	132.4	132.5	133.4	
5	143.6	140.1	140.2	139.8	139.3	139.9	
6	175.8	176.8*	171.8	171.1	170.7	171.9	
7	84.8	85.5	86.3	85.4	84.6	85.6	82.9
8	70.4	65.3	66.0	65.4	65.3	71.7	64.2
9	74.2	74.0‡	75.5	74.8	74.5	75.6	74.8
10	83.7	72.1	72.4	71.7	71.2	83.7	71.8
11	36.5	75.4‡	74.5	73.7	73.2	37.3	73.7
12	97.3	82.3	82.0	81.7	81.7	98.5	82.0
13	56.1	57.2	56.4	56.3	56.6	56.1	56.1
14	168.3*,[b]	159.4*,[b]	159.8	158.9	159.7	159.1	
15	160.2†	161.0†	156.2*	156.2	161.9	154.9*	
16	140.9	141.4°	142.1	140.3*	85.8	86.4	
17	114.6	115.5	126.4	125.5	37.9	38.1	
18	114.6	115.5	164.8	160.9			
19	162.9*,[b]	169.4*,[b]	169.3	169.3	118.8	121.1	
20	158.6†	163.8†	158.6*	152.5	151.6	162.0*	
21	138.8	144.0	131.0	131.4	135.7	137.4	
22	19.8	20.3	20.0	17.4	25.0	27.4	
23	140.9	141.6°	142.1	140.9*	141.7	143.7	
24	140.9	141.6°					
25	27.0	27.3					
26	67.3	67.8					
27	85.7	86.2					
28	39.6	39.8					
29	50.2	50.7					
30	136.4	137.4					
31	131.8	133.1					
32	136.9					138.6	
33					177.6	175.4	

[a] All shifts are in parts per million upfield from CS_2. [b] These assignments reflect a greater sensitivity of the C-19 resonances to shift reagents than those of the C-14 carbons. *, ‡, †, ° represent signals where the assignments may be reversed.

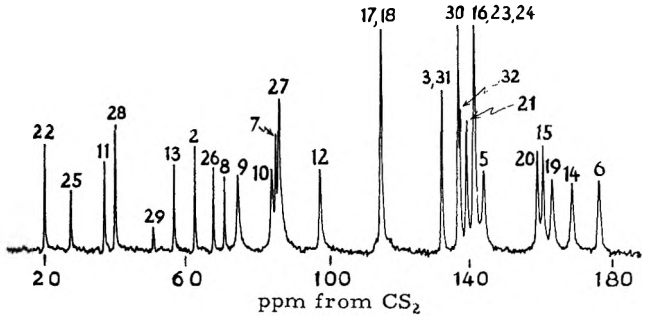
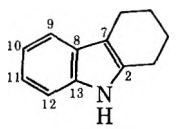


Figure 1.—A PFT ^{13}C nmr spectrum of reserpine (I) in deuteriochloroform. The spectral width was 5000 Hz, 5500 transients, with an acquisition time of 0.4 sec. The plot has 2.5 Hz per spectral data point. The numbers beside each peak correspond to the assignments of Table I.

increasing frequency,[13] it becomes easier to make relatively accurate assignments on the basis of the observed chemical shifts. The ^{13}C nmr signals of the indole rings of compounds II–V could be readily identified by direct comparison to the ^{13}C nmr spectrum of tetrahydrocarbazole (VII). As is shown in Table I,



VII

the aromatic and unsaturated resonances of tetrahydrocarbazole display chemical shifts which are very similar to those of the corresponding carbon atoms in II–V, and the sequence of chemical shifts for the carbon atoms in VII is maintained throughout with II–V.

The effect of methoxy groups on ^{13}C nmr shifts has been studied previously.[14] In an extension of this work, we have found the effect in a variety of aromatic substances to be quite regular and predictable. A methoxy substituent shifts a para carbon atom *ca.* 6.8 ppm to higher field, a meta carbon *ca.* 2.4 ppm to lower field, and an ortho carbon *ca.* 15.0 ppm to higher field, as compared to the unsubstituted aromatic compound. If the ortho carbon bears a substituent, then the upfield shift is reduced from 15.0 ppm to *ca.* 8.8 ppm. The methoxylated carbon atom itself is shifted *ca.* 31.3 ppm downfield from where it would come into resonance, were it unsubstituted. If several methoxy groups are present, then their effects are approximately additive. Using deserpidine (II) as a model compound, the chemical shifts for the corresponding carbon atoms in reserpine (I) can be predicted by using the above values (Table IV). The predicted shifts are not highly accurate but the predicted values are in the correct sequence and are accurate enough to facilitate making assignments. The trimethoxybenzoic acid residues in I and II were also analyzed in an analogous fashion with comparable success.

(13) See, for example, P. S. Pregosin and E. W. Randall in "Determination of Organic Structures by Physical Methods," Vol. IV, F. C. Nachod and J. J. Zuckerman, Ed., Academic Press, New York, N. Y., 1971.

(14) P. C. Lauterbur, *J. Amer. Chem. Soc.*, **83**, 1846 (1961); H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 731 (1961).

TABLE II

SINGLE-FREQUENCY OFF-RESONANCE RESULTS[a]

Carbon	I	III	IV	V
2	ST	ST	ST	ST
3	DQ	DQ	DQ	DQ
5	ST	ST	ST	ST
6	ST	ST	ST	ST
7	ST	ST	ST	ST
8	ST	ST	ST	ST
9	DQ	DQ	DQ	DQ
10	DQ	DQ	DQ	DQ
11	ST	DQ	DQ	DQ
12	DQ	DQ	DQ	DQ
13	ST	ST	ST	ST
14	ST	ST	ST	ST
15	DQ	DQ	DQ	DQ
16	DQ	DQ	DQ	ST
17	DQ	DQ	DQ	DQ
18	DQ	ST	ST	
19	ST	ST	ST	DQ
20	DQ	DQ	DQ	DQ
21	ST	ST	ST	ST
22	ST	ST	ST	ST
23	DQ	DQ	DQ	DQ
24	DQ			
25	ST			
26	ST			
27	DQ			
28	ST			
29	ST			
30	DQ			
31	DQ			
32	DQ			
33				DQ

[a] ST = singlet or triplet; DQ = doublet or quartet.

All of the resonances below 130 ppm could be assigned readily to specific carbon atoms, with the SFOR results being used to remove occasional ambiguities or merely to corroborate the postulated assignments. It is to the high-field side of 130 ppm that serious problems in assignment were encountered, as this region contains the majority of the aliphatic carbon resonances which are often methylene carbons, with nonequivalent protons expected to provide further difficulties in the use of the SFOR technique. In order to present some idea of the complexity involved, we note that reserpine (I) has, besides five methylene carbons, six methyne carbons and five methoxy carbons, all of which are different and expected to absorb in this area. It was easy to distinguish the resonances of those aliphatic carbon atoms connected directly to oxygen or nitrogen from those not so substituted. For the latter, the SFOR experiments provided some further clarification but, in general, a variety of unresolved assignments remained. For example, it was not possible to assign the five different methoxy carbons in I to specific signals on the basis of chemical-shift considerations alone.

A partial solution to this dilemma was achieved with paramagnetic lanthanide chelate shift reagents.[11,15] Because the bulk of functional groups in alkaloids I–VI are localized in one portion of the molecule, it was anticipated that, in accord with the $[(3\cos^2\theta - 1)/r^3]$ formalism, the shifts of those carbon atoms located farthest from this complexation area should display the lowest sensitivity to variations in shift reagent concentrations (provided, of course, that θ is small, as it usually seems to be). Carbon atoms located in the immediate vicinity of the complexation site should exhibit an increased sensitivity to chelate concentration, while the other carbons would be expected to display intermediate behavior.

(15) E. Wenkert, D. W. Cochran, E. W. Hagaman, R. B. Lewis, and F. M. Schell, *J. Amer. Chem. Soc.*, **93**, 6271 (1971), and references cited therein.

TABLE III

LANTHANIDE INDUCED CHEMICAL-SHIFT CHANGES[a,b]

Carbon	I	IV	V
2	0.9	0.2	1.8
3	5.3	0.4	2.0
5	0.8	0.0	0.8
6	0.3	0.0	0.9
7	0.1	−0.4[c]	1.0
8	0.3	0.0	0.6
9	0.1	0.0	0.5
10	0.1	0.0	0.4
11	0.3	0.0	0.4
12	0.2	0.0	0.6
13	0.5	0.0	0.9
14	1.5	0.5	5.0
15	1.1	1.0	4.3
16	3.5*	1.2	6.6
17	4.5	3.3	3.0
18	5.5	1.3	
19	1.8	1.1	0.9
20	1.7	0.5	2.0
21	0.9	0.3	1.0
22	2.8	2.2	6.7
23	3.5*	0.9	5.6
24	1.0*		
25	4.4		
26	5.6		
27	5.8		
28	14.9		
29	24.1		
30	8.0		
31	16.6		
32	0.2		
33			0.4

[a] Shifts are in parts per million upfield from the resonance position in the absence of shift reagent. [b] Values are for $\{[Pr(FOD)_3]/[alkaloid]\} = 0.5$. [c] A minus sign indicates a downfield shift. * Represents assignments which may be reversed.

TABLE IV

CALCULATED CARBON 13 CHEMICAL SHIFTS FOR RESERPINE (I)[a]

Carbon	II (model)	I (predicted)	I (observed)
8	65.3	72.1	70.4
9	75.4	73.0	74.2
10	72.1	87.1	83.7
11	74.0	42.7	36.5
12	82.3	97.3	97.3
13	57.2	54.8	56.1

[a] All shifts are in parts per million upfield from CS_2.

Lanthanide shift measurements with reserpine (I) have been particularly illuminating. We present here a few selected results to demonstrate the applicability of the lanthanide shift technique to the ^{13}C nmr spectra of large, multifunctional molecules. The noise-decoupled ^{13}C nmr spectrum of reserpine is shown in Figure 1. Reserpine contains 30 different carbon atoms, 16 of which are expected to come into resonance below 120 ppm. However, only 15 absorptions are present,

with 11 more being apparent above 120 ppm. Thus, there are four carbon atoms which are accidentally equivalent with other carbon atom(s). Gradual addition of the lanthanide chelate, $Pr(FOD)_3$, led to the eventual appearance of 29 of the 30 possible signals. The five methoxy carbons in reserpine (I) were located at 131.8, 136.4, 136.9, and 140.9 (2) ppm by chemical shift, intensity, and SFOR considerations. The signals at 131.8, 136.4, and 140.9 ppm were of greater intensity than most other peaks in the ^{13}C nmr spectrum of I, indicating possible degeneracy. Addition of the shift reagent produced two resonances from the 131.8- and 140.9-ppm signals, the 136.4-ppm absorption still remaining singular and unreduced in intensity. One of the peaks at 131.8 ppm was assigned to a nonmethoxyl carbon (C-3). The high-intensity signal at 136.4 ppm was assigned to the two isochronous C-30 methoxy carbon atoms. Because of its dramatic sensitivity to shift-reagent concentration, the other component of the 131.8-ppm resonance is assigned to the methoxy carbon, C-31. Of all the carbon atoms of I, C-29 displays the greatest sensitivity to lanthanide chelate concentration (Table III) and is followed in this respect by C-31, C-28, and C-30, in that order. The results suggest that the shift reagent complexes with reserpine preferentially, although probably by no means exclusively, at the oxygen which is connected to C-29. Because C-23 and C-24 are closer to the complexation site than C-32, we expect them to have an appreciably greater sensitivity to shift-reagent concentration than C-32 and therefore attribute two of the three components of the 140.9-ppm signal to C-23 and C-24. C-32 is then assigned to the signal at 136.9 ppm which shows, as expected, a diminished sensitivity to shift reagent concentration.

Further application of the above procedures to alkaloids I–VI has led to the other assignments given in Table I, which will not be discussed in detail. It seems clear that PFT ^{13}C nmr will play an increasingly important role in the structural analysis of natural products.

Experimental Section

The ^{13}C spectra were obtained using a "Brukarian" pulsed FT spectrometer which was the previously described[6,16] Varian digital frequency sweep instrument operating at 15.09 MHz, but modified by substitution of a Bruker pulse amplifier, probe, receiver, and internal deuterium lock. The pulses were derived from a Varian pulse box, and the free-induction decay was accumulated and transformed with a 16K Varian 620i computer.[17]

All of the alkaloids, except corynanthine (III), were dissolved in chloroform-*d* to yield 0.5–2.0 *M* solutions. Corynanthine was dissolved in chloroform-*d* containing a small amount of ethanol to enhance solubility. The spectra were referenced to external carbon disulfide by the relationship $\delta_C^{CS_2} = \delta_C^{CDCl_3} + 115.4$ ppm.

Registry No.—I, 50-55-5; II, 131-01-1; III, 483-10-3; IV, 146-48-5; V, 483-04-5; VI, 482-96-2; VII, 942-01-8.

Acknowledgment.—We thank Dr. M. W. Klohs of Riker Laboratories, Inc., for supplying us with samples of many of the Rauwolfia alkaloids used in this research.

(16) F. J. Weigert and J. D. Roberts, *J. Amer. Chem. Soc.*, **89**, 2967 (1967).

(17) We are much indebted to Dr. Bruce Hawkins for his help in the development of this spectrometer system.

Stable Carbocations. CXLIX.[1] Fourier Transform Carbon-13 Nuclear Magnetic Resonance Spectroscopic Study of Protonated Mono- and Dicarboxylic Acid Esters in FSO_3H–SbF_5 Solution

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The ^{13}C nmr chemical shifts for a series of protonated aliphatic carboxylic acid esters were determined in FSO_3H–SbF_5 solution together with those of their parent esters. Protonation of esters results in deshielding of the carbonyl carbon resonance of the order of 17–21 ppm, of the carbons α to the alkyl oxygen, 12–23 ppm, and those α to the carbonyl group, 0–3 ppm. At the same time generally a slight shielding of most other carbon resonances is observed. The results have been correlated with other substituent effects and with ^{13}C resonances in corresponding hydrocarbons. The pmr and cmr spectra of several protonated diesters in FSO_3H–SbF_5 at $-60°$ have also been studied. The results indicate that dicarboxylic acid esters, including those of oxalic acid, are diprotonated under these conditions.

Several recent instrumental developments in both slow passage and pulsed nuclear magnetic resonance spectrometers[3,4] have allowed for the routine determination of ^{13}C chemical shifts at ^{13}C natural abundance.[5]

The ^{13}C spectra of several carboxylic acids and their tetramethylammonium salts have been recorded in aqueous solution by Hagan and Roberts.[6] Using the INDOR technique[7] in our previous work, we obtained the ^{13}C spectra of protonated formic, acetic, propionic, and benzoic acids in FSO_3H–SbF_5 solution.[8] Carboxylic acid esters and their protonated derivatives have been examined by ^{13}C nmr spectroscopy to a much lesser extent. The carbonyl carbon shifts for a series of carboxylic acid esters have been reported[9] as well as

(1) Part CXLVIII: G. A. Olah and G. Liang, *J. Amer. Chem. Soc.*, **95**, 3792 (1973).

(2) Postdoctoral Research Fellow, 1971–1973.

(3) F. J. Weigert and J. D. Roberts, *J. Amer. Chem. Soc.*, **89**, 2967 (1967).

(4) T. C. Farrar and E. D. Becker, "Pulse and Fourier Transform NMR," Academic Press, New York, N. Y., 1971, pp 34–45.

(5) For example, see (a) J. B. Grutzner, M. Jautelat, J. B. Dence, R. A. Smith, and J. D. Roberts, *J. Amer. Chem. Soc.*, **92**, 7107 (1970); (b) A. J. Jones, D. M. Grant, M. W. Winkley, and R. K. Robins, *ibid.*, **92**, 4079 (1970); (c) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *ibid.*, **92**, 1338 (1970); (d) F. J. Weigert and J. D. Roberts, *ibid.*, **92**, 1347 (1970).

(6) R. Hagen and J. D. Roberts, *ibid.*, **91**, 4504 (1969).

(7) E. B. Baker, *J. Chem. Phys.*, **37**, 911 (1962).

(8) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, **89**, 7072 (1967).

(9) J. B. Stothers and P. C. Lauterbur, *Can. J. Chem.*, **42**, 1563 (1964).

TABLE I

^{13}C CHEMICAL SHIFTS[a] OF ALIPHATIC ESTERS

No.	Registry no.	Ester	Carbonyl	R—C=O				—O—R		
				C_α	C_β	C_γ	C_δ	C_α	C_β	C_γ
1	107-31-3	Methyl formate	32.0					143.1		
2	79-20-9	Methyl acetate	23.1	173.3						
			23.0[b]	173.2[c]				142.2		
			21.0[c]					141.4[c]		
3	554-12-1	Methyl propionate	19.6	165.5	183.8			141.8		
4	623-42-7	Methyl butyrate	20.6	157.2	173.9	179.0		141.3		
5	624-24-8	Methyl valerate	19.4	157.9	164.3	168.9	177.7	141.2		
			17.5[c]	158.0[c]	164.4[c]	169.0[c]	177.6[c]	139.9[c]		
6	109-94-4	Ethyl formate	33.5					134.8	180.3	
			33.0[b]							
7	141-78-6	Ethyl acetate	23.8	172.7				133.1	178.8	
			22.9[b]	172.1				131.6[c]	178.6[c]	
			21.0							
8	105-37-3	Ethyl propionate	20.4	165.4	183.8			133.1	178.6	
			17.6[c]	165.3[c]	183.6[c]			131.7[c]	178.6[c]	
9	105-54-4	Ethyl butyrate	21.2	156.6	173.9	179.0		133.1	178.3	
10	625-55-8	Isopropyl formate	33.2					125.6	171.4	
11	108-21-4	Isopropyl acetate	23.5	173.3				125.2	171.2	
12	105-46-4	*sec*-Butyl acetate	24.2	173.3				121.2	163.6 (CH_2)	183.0
									171.9 (CH_3)	
13	540-88-5	*tert*-Butyl acetate	24.2	170.5				113.4	164.4	
14	598-98-1	Methyl pivalate	16.2	154.2	165.6			141.7		
15	547-63-7	Methyl isobutyrate	19.3	161.8	176.6			143.0		
16	97-62-1	Ethyl isobutyrate	18.5	158.5	173.7			133.0	178.3	
			15.1[c]	158.6[c]	173.8			131.7[c]	178.6[c]	
17	95-92-1	Diethyl oxalate	36.1					130.7	179.6	
18	105-52-3	Diethyl malonate	27.1	151.3				131.8	178.7	
19	123-25-1	Diethyl succinate	21.7	163.6				132.5	178.5	
20	818-38-2	Diethyl glutarate	21.2	159.5	172.2			132.8	178.5	
21	6279-86-3	Tricarboethoxymethane	31.5	135.7				132.6	180.8	
22	39000-70-9	Tetracarboethoxymethane	33.0	121.3				131.8	180.8	

[a] In parts per million (ppm) relative to $^{13}CS_2$. [b] Reference 9. [c] 20% (v/v) in SO_2 at −60°.

the methyl carbon shifts in a number of methyl esters.[10] In our previous studies,[11,12] we reported the ^{13}C nmr spectrum of a single ester, *i.e.*, methyl acetate. We felt it, therefore, of interest to extend these data by undertaking a systematic cmr study of protonated and parent esters, using the Fourier transform cmr method.

Results and Discussion

Protonated Monocarboxylic Acid Esters.—To extend our knowledge of the structure of protonated carbonyl compounds we undertook the cmr study of a series of protonated esters in the superacid system FSO_3H–SbF_5, and for comparison, their parent compounds. The chemical shift data obtained using pulsed nmr with Fourier transformation techniques[4,13] are summarized in Tables I and II.

The assignment of resonances was made by the now familiar procedures of Grant and coworkers.[14,15] These include use of the observation that a polar group exerts a large inductive effect on the shift of a directly attached carbon, and, if elements of symmetry are present in a molecule, it is possible to assign signals on the basis of relative intensities. Also, for closely grouped methylene resonances, minimal substituent effects can be assumed with respect to the corresponding hydrocarbons. Assignment of some signals was made by comparison of the carbon shifts for a particular ester with those of the homolog containing one less carbon atom. For example, the two methyl carbon resonances of ethyl acetate can be distinguished by comparing its spectrum with that of ethyl formate. To be assured of the correct assignment in a number of cases it was necessary to conduct "off-resonance" decoupling experiments.

The ^{13}C chemical shifts shown in Table I are given with reference to carbon disulfide, but were in fact experimentally measured from external methyl iodide. Details of the method by which chemical shifts were determined, as well as a description of the nmr instrumentation, are provided in the Experimental Section. Consistent with the usual conventions, positive values in Tables I and II represent chemical shifts shielded from carbon disulfide, whereas negative values are more deshielded in regard to the reference. ^{13}C nmr spectra of the parent esters were recorded neat at 30–35°, and in several cases at −60° in SO_2 solution. Only the carbonyl carbon shifts and the carbons α to the alkyl oxygen were found to differ by more than ±0.3 ppm in the two media. Solvent effects on carbonyl ^{13}C shifts in aprotic solvents have been interpreted in terms of carbonyl π-bond polarity as influenced by polar and van der Waals interactions with the solvent.[16] Our present experimental results may indicate slight solvent–solute interactions between the ester carbonyl groups

(10) W. McFarlane, *J. Chem. Soc. B*, 28 (1969).
(11) G. A. Olah, D. H. O'Brien, and A. M. White, *J. Amer. Chem. Soc.*, **89**, 5694 (1967).
(12) G. A. Olah and A. M. White, *ibid.*, **91**, 5801 (1969).
(13) R. R. Ernst and W. A. Anderson, *Rev. Sci. Instrum.*, **37**, 93 (1966).
(14) D. M. Grant and E. G. Paul, *J. Amer. Chem. Soc.*, **86**, 2984 (1964).
(15) D. K. Dalling and D. M. Grant, *ibid.*, **89**, 6612 (1967).
(16) G. E. Maciel and J. J. Natterstad, *J. Chem. Phys.*, **42**, 2752 (1965).

TABLE II

^{13}C CHEMICAL SHIFTS[a] OF PROTONATED ALIPHATIC ESTERS

No.	Registry no.	Compound	Carbonyl	R—C=O				O—R		
				C_α	C_β	C_γ	C_δ	C_α	C_β	C_γ
1	39014-35-2	$H[C(OH)OCH_3]^+$	14.4					125.7		
2	39014-36-3	$CH_3[C(OH)OCH_3]^+$	1.8	171.6				126.5		
3	39014-37-4	$CH_3CH_2[C(OH)OCH_3]^+$	−0.7	164.0	185.5			129.4		
4	39014-38-5	$CH_3CH_2CH_2[C(OH)OCH_3]^+$	0.0	156.5	175.2	179.8		129.4		
5	39014-39-6	$CH_3CH_2CH_2CH_2[C(OH)OCH_3]^+$	−0.1	158.3	167.1	170.7	179.3	129.3		
6	39014-40-9	$H[C(OH)OCH_2CH_3]^+$	15.7					115.4	179.6	
7	39014-41-0	$CH_3[C(OH)OCH_2CH_3]^+$	2.7	171.3				116.8	179.5	
8	39014-42-1	$CH_3CH_2[C(OH)OCH_2CH_3]^+$	0.4	163.6	185.5			116.2	179.5	
9	39014-43-2	$CH_3CH_2CH_2[C(OH)OCH_2CH_3]^+$	1.3	156.5	175.3	179.8		116.5	180.0	
10	39532-21-3	$H[C(OH)OCH(CH_3)_2]^+$	16.6					102.2	172.2	
11	39014-44-3	$CH_3[C(OH)OCH(CH_3)_2]^+$	2.8	171.9				102.3	172.2	
12	39014-45-4	$CH_3[C(OH)OCH(CH_3)CH_2CH_3]^+$	3.5	172.0				99.6	164.5 (CH_2)	183.5
									174.4 (CH_3)	
14	39014-46-5	$(CH_3)_3C[C(OH)OCH_3]^+$	−4.7	151.5	167.2			128.7		
16	39014-47-6	$(CH_3)_2CH[C(OH)OCH_2CH_3]^+$	2.0	157.0	175.2			116.4	179.9	
17	39014-48-7	$[C(OH)OCH_2CH_3]_2^{2+}$	28.1					105.3	179.1	
18	39014-49-8	$CH_2[C(OH)OCH_2CH_3]_2^{2+}$	12.9	151.2				111.2	179.4	
19	39014-50-1	$(CH_2)_2[C(OH)OCH_2CH_3]_2^{2+}$	5.1	163.7				113.2	179.6	
20	39014-51-2	$(CH_2)_3[C(OH)OCH_2CH_3]_2^{2+}$	2.7	159.4	175.6			113.8	179.3	

[a] In parts per million (ppm) relative to $^{13}CS_2$.

and sulfur dioxide, but the effect is small and is not the major contribution to the large downfield shift that occurs for the carbonyl ^{13}C shift on oxygen protonation.

^{13}C chemical shifts of the protonated esters were measured at −60° in excess of FSO_3H–SbF_5 solution, using SO_2 as diluent.

In order to evaluate the effect of substituents on the chemical shift of a particular carbon atom in a molecule, it is customary to subtract the shift of the corresponding carbon of the unsubstituted parent hydrocarbon from the shift of the same carbon in the substituted hydrocarbon.[17,18] We have used this procedure to evaluate the substituent effects of the carboalkoxy and protonated carboalkoxy groups on both the alkoxy and acyl carbon shifts in the esters of Tables I and II. The validity of this approach in our present study, with the very large difference in environment in which the shifts of the unsubstituted and substituted hydrocarbons were measured is questionable. However, the results show that the substituent effects of the carboalkoxy and protonated carboalkoxy groups follow trends very much like those caused by the hydroxyl,[5a] keto,[5d] and carboxyl[6] groups in nonrigid systems and by a large number of substituents in the rigid norbornyl system.[5a] The α-substituent effect for the monoesters in Table III is always deshielding, being from 46.6 to 54.2 ppm for the RCOO– group and from 20.0 to 24.4 ppm for the –COOR group.

The α-substituent effect of a –COOR group on a particular carbon resonance is not this value if several –COOR groups are already attached to that carbon. Thus, inspection of the shift data in Tables I and III for ethyl acetate, ethyl malonate, tricarboethoxymethane, and tetracarboethoxymethane shows that the methane ^{13}C chemical shift is progressively deshielded 22.2, 21.4, 15.6, and 14.7 ppm by the successive replacement of the hydrogens with –COOR groups. Similar variations in the methane carbon shift, brought about by the successive replacement of hydrogens by substituent, have been extensively studied.[17,19,20] Nonlinearity in plots of chemical shift *vs.* degree of substitution, such as are observed for bromine and iodine, have been interpreted[17] in terms of an increasing neighbor anisotropy contributions to the carbon shift, as more substituents are added to the molecule. Recently, it has been claimed[20] that the failure to interpret these experimental plots in terms of simple additive relationships is a result of not allowing a diamagnetic correction.

The RCOO– group has almost the same α effect as the hydroxyl group in corresponding aliphatic alcohols (Table IV of ref 5a) with values for the alcohols consistently smaller by 2–3 ppm. This difference may be a result of the greater electronegativity[21] of the RCOO– functional group compared with the –OH group, a deshielding effect associated with the anisotropy of the carbonyl group, or a solvent effect. Similarly the ROOC– functional group has almost the same α effect as that of the HOOC– group (Table II of ref 6) with the latter causing the greater deshielding. The α substituent effect of the ROOC– group, however, is much smaller than that of the RCOO– group.

The increments caused by β carbons are also negative, and comparison of the results in Table III with those for the corresponding alcohols[5a] and carboxylic acids[6] show an effect of almost the same magnitude in both cases. The RCOO– functional group has a slightly

(17) H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 722 (1961).
(18) E. G. Paul and D. M. Grant, *J. Amer. Chem. Soc.*, **86**, 2977 (1964).
(19) P. C. Lauterbur, *Ann. N. Y. Acad. Sci.*, **70**, 841 (1958).
(20) J. Mason, *J. Chem. Soc. A*, 1038 (1971).
(21) One definition of electronegativity is that provided by Dailey and Shoolery [*J. Amer. Chem. Soc.*, **77**, 3977 (1955)]

$$\text{electronegativity} = 0.684\delta_{\text{internal}} + 1.78$$

where δ_{internal} is the difference in chemical shift between the methyl and methylene protons of the appropriately substituted ethane derivative. Inspection of the pmr data[22] for ethyl acetate and ethanol show that δ_{internal} is slightly larger for the first compound. The RCOO– group is, therefore, more electronegative than the HO– group. The pmr data for ethyl acetate and methyl propionate show that δ_{internal} is larger for the first compound and thus the RCOO– group is also more electronegative than the –COOR group according to this definition. By a similar argument (see ref 11 for pmr data) the $RC(OH)^+O$– group is more electronegative than the $-C(OH)^+OR$ group.
(22) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 164.

TABLE III

^{13}C CHEMICAL SHIFT[a] DIFFERENCE BETWEEN ESTERS AND THEIR CORRESPONDING UNSUBSTITUTED HYDROCARBONS[b]

		R—C=O				O—R		
No.	Compound	C_α	C_β	C_γ	C_δ	C_α	C_β	C_γ
1	Methyl formate					−51.8		
2	Methyl acetate	−21.6				−52.7		
3	Methyl propionate	−21.4	−3.1			−53.1		
4	Methyl butyrate	−20.0	−2.8	1.8		−53.6		
5	Methyl valerate	−21.7	−3.5	1.1	−1.9	−53.7		
6	Ethyl formate					−52.1	−6.6	
7	Ethyl acetate	−22.2				−53.8	−8.1	
8	Ethyl propionate	−21.5	−3.1			−53.8	−8.3	
9	Ethyl butyrate	−20.6	−2.8	1.8		−53.8	−8.6	
10	Isopropyl formate					−51.1	−5.8	
11	Isopropyl acetate	−21.6				−51.5	−6.0	
12	*sec*-Butyl acetate	−21.6				−46.6	−4.2 (CH_2)	3.4
							−7.7 (CH_3)	
13	*tert*-Butyl acetate	−24.4				−54.2	−4.1	
17	Diethyl oxalate					−56.2	−7.3	
18	Diethyl malonate	−43.6						
		(−21.4)[c]				−55.1	−8.2	
19	Diethyl succinate[d]	−20.0				−54.4	−8.4	
20	Diethyl glutarate[e]	−19.5				−54.1	−8.4	
21	Tricarboethoxymethane	−59.2				−54.3	−6.1	
22	Tetracarboethoxymethane	−73.6				−55.1	−6.1	

[a] In parts per million (ppm). Negative sign indicates a deshielding. [b] The differences were calculated by subtracting the chemical shifts of an aliphatic ester from the shifts in the corresponding unsubstituted hydrocarbon.[18] [c] Shift increment calculated using ethyl acetate as model compound. [d] Shift increment calculated using ethyl propionate as model compound. [e] Shift increment calculated using ethyl butyrate as model compound.

TABLE IV

^{13}C CHEMICAL SHIFT[a] DIFFERENCES BETWEEN PROTONATED ESTERS AND THEIR CORRESPONDING UNSUBSTITUTED HYDROCARBONS[b]

		R—C=O$^+$—H				O—R		
No.		C_α	C_β	C_γ	C_δ	C_α	C_β	C_γ
1						−69.2		
2		−23.3				−68.4		
3		−22.9	−1.1			−65.5		
4		−20.7	−1.5	2.6		−65.5		
5		−21.3	−0.7	2.9	−0.3	−65.6		
6						−71.5	−7.3	
7		−23.6				−70.1	−7.4	
8		−23.3	−1.4			−70.7	−7.4	
9		−20.7	−1.4	2.6		−70.4	−6.9	
10						−74.5	−5.0	
11		−23.0				−74.4	−5.0	
12		−22.9				−68.1	−3.3 (CH_2)	3.9
							−5.2 (CH_3)	
14		−16.1	−1.3			−66.2		
16		−19.7	−2.0			−70.5	−7.0	

[a] In parts per million (ppm). Negative sign indicates a deshielding. [b] The differences were calculated by subtracting the chemical shifts of an aliphatic ester from the shifts in the corresponding unsubstituted hydrocarbon.[18]

smaller effect than the hydroxyl group, but, as the factors which contribute to the β effect are less well understood than those which contribute to the α effect,[23,24] an explanation will not be attempted.

Table III shows a γ effect, for the RCOO– and –COOR groups, of the same magnitude and sign (positive) as that of the hydroxyl[5a] and carboxyl[6] groups. These same two groups have a negative δ effect,[5a,6] which is also the case for the sole δ effect recorded in Table III. As expected the magnitude of the substituent effect for both –COOR and RCOO– groups falls off rapidly with increasing chain length.

Inspection of Table IV shows that most of the above observations are also applicable to the protonated –COOR and RCOO– groups. The variations of the shielding of carbons α to most substituents are apparently dominated by the electronegativity of the substituent.[17,19,25,26] The protonated carboalkoxy group is substantially more electronegative than the carboalkoxy group,[21] and one would therefore expect a deshielding of the α carbons on protonation of a carboxylic acid ester. This is found to be the case for the carbon nuclei α to the carbonyl group, which are deshielded 0.1 to 2.7 ppm as well as those α to the alkyl oxygen (15.4 to 23.4 ppm). The greater electronegativity of the RC(OH)$^+$O– group compared with the –C(OH)$^+$OR group

(23) B. V. Cheney and D. M. Grant, *J. Amer. Chem. Soc.*, **89**, 5319 (1967).
(24) D. M. Grant and B. V. Cheney, *ibid.*, **89**, 5315 (1967).
(25) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution NMR Spectroscopy," Pergamon Press, Oxford, 1965, pp 136–138, 992–999.
(26) W. M. Litchman and D. M. Grant, *J. Amer. Chem. Soc.*, **90**, 1400 (1968).

TABLE V

^{13}C CHEMICAL SHIFT[a] DIFFERENCES BETWEEN PROTONATED ESTERS AND THEIR PARENTS[b]

No.	Ester	R—C=O				O—R				$\Delta\delta_{^{13}C=O} + \Delta\delta_{O-^{13}CH_3}$
		C_α	C_β	C_γ	C_δ	C_α	C_β	C_γ	Carbonyl	
1	Methyl formate					−17.4			−17.6	−35.0
2	Methyl acetate	−1.7				−15.7			−21.3	−37.0
3	Methyl propionate	−1.5	2.0			−12.4			−20.3	−32.7
4	Methyl butyrate	−0.7	1.2	0.8		−11.9			−20.6	−30.8
5	Methyl valerate	−0.4	2.8	1.8	1.6	−11.9			−19.5	−31.4
6	Ethyl formate					−19.4	−0.7		−17.8	−37.2
7	Ethyl acetate	−1.4				−16.3	0.7		−21.1	−37.4
8	Ethyl propionate	−1.8	1.7			−16.9	0.9		−20.0	−36.9
9	Ethyl butyrate	−0.1	1.4	0.8		−16.6	1.7		−19.9	−36.5
10	Isopropyl formate					−23.4	0.8		−16.6	−40.0
11	Isopropyl acetate	−1.4				−22.9	1.0		−20.7	−43.6
12	*sec*-Butyl acetate	−1.3				−21.5	0.9 (CH_2)	0.5	−20.7	−42.2
							2.5 (CH_3)			
14	Methyl pivalate	−2.7	1.6			−13.0			−20.9	−33.9
16	Ethyl isobutyrate	−1.5	1.5			−16.6	1.6		−20.5	−37.1
17	Diethyl oxalate					−25.4	0.5		−8.0	−33.4
18	Diethyl malonate	−0.1				−20.6	0.8		−14.2	−34.8
19	Diethyl succinate	+0.1				−19.3	1.1		−16.6	−35.9
20	Diethyl glutarate	−0.1	3.4			−19.0	0.8		−18.5	−37.5

[a] In parts per million (ppm). Negative sign indicates a deshielding. [b] Differences calculated by subtracting the chemical shifts of the protonated esters from the corresponding shifts in the parent ester.

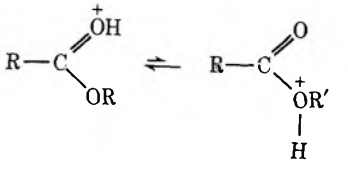
must be partly responsible for the greater deshielding of the latter α carbons. Inspection of Table V reveals that the greatest deshielding on ester protonation of carbons α to an alkyl oxygen occurs for isopropyl acetate, *sec*-butyl acetate, and isopropyl formate (22.9, 21.5, and 23.4 ppm, respectively). Furthermore, the deshielding of the α carbon, on protonation, increases in the series methyl, ethyl, and isopropyl acetate, as well as in the series methyl, ethyl, and isopropyl formate. This may reflect an increasing relative contribution of mesomer III in the protonated esters of secondary alcohols compared with those or primary alcohols.

The β, γ, and δ resonances become more shielded on protonation of esters (Table V). This may simply be a solvent effect. It is interesting to note that the shielding of the β-, γ-, and δ-carbon resonances changes in the opposite direction on carbonyl oxygen protonation to that of the proton resonances.[11] This is similar to the observations of Hagan and Roberts,[6] for carboxylic acids and their carboxylate anions, where ionization of the acids resulted in the expected shielding of the proton resonances, but deshielding of the carbon resonances.

Protonation of esters results in a deshielding of the carbonyl carbon resonances of 16.6 to 21.3 ppm (Table V). Deshielding of the carbonyl carbon resonances in esters has been observed by Maciel and Natterstad[16] for solvents capable of hydrogen bonding to the carbonyl oxygen. They gave several possible interpretations[16,27] of the observed deshieldings, principally in terms of changes in the carbonyl π-bond polarity.

The carbonyl chemical shift values in Table I are subject to a methyl substituent effect. Replacement of the carbonyl hydrogen in a formate ester by a methyl group results in the carbonyl carbon being deshielded approximately 9 ppm. Hence, the observed α-methyl substituent effect is of comparable magnitude to that in carbonyl compounds (5–8 ppm)[9] and carboxylic acids (11 ppm).[9] An α-methyl substituent effect (12–14 ppm) on the carbonyl carbon shift in protonated esters is also indicated by a comparison of the data for protonated formates and acetates (Table II). Similar comparisons (Table I) between acetates and propionates and between propionates and butyrates show a β-methyl substituent effect, that is deshielding (3.4 ± 0.1 ppm), and a γ-methyl substituent effect, that is shielding (0.8 ± 0.1 ppm). The corresponding substituent effects in protonated esters are of the same sign as for their parents and are 2.4 ± 0.1 ppm and 0.8 ± 0.1 ppm, respectively. Examination of the carbonyl chemical shifts in protonated and unprotonated methyl pivalate, methyl and ethyl isobutyrate show that the α and β effects are approximately additive. However, there is insufficient data in Tables I and II to summarize these observed α-, β-, and γ-methyl substituent effects by a relationship, similar to that used by Grant and Paul[14] for straight-chain and branched hydrocarbons.

None of the studied protonated esters, including the secondary alkyl esters which showed increased tendency of cleavage on standing even at low temperature, gives indication of ether oxygen protonation. As in acid-catalyzed ester hydrolysis the intermediacy of the ether oxygen protonated acylalkyloxonium ion is generally assumed, the latter could be formed in a minimal equilibrium from the carbonyl oxygen protonated form



Alternatively it is possible that in excess superacid as solvent system, carbonyl oxygen protonated esters can undergo a second protolytic attack on the ether oxygen unshared electron pairs leading to a highly destabilized

(27) G. E. Maciel, *J. Chem. Phys.*, **42**, 2746 (1965).

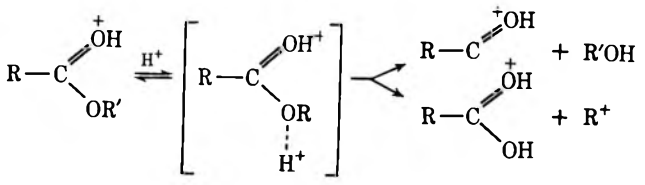
TABLE VI

PMR CHEMICAL SHIFTS[a] OF DIPROTONATED DICARBOXYLIC ACID ESTERS IN FSO_3H–SbF_5–SO_2 AT −60°

Ester	=O—H	R—C=O Cα	R—C=O Cβ	—O—R Cα	—O—R Cβ
Diethyl oxalate				1.98 (0.53)[b]	5.90 (1.55)
Diethyl malonate	14.6[c]	5.15 (1.65)		2.02 (0.63)	5.58 (1.25)
Diethyl succinate	13.26	3.94 (1.19)		2.02 (0.60)	5.51 (1.25)
Diethyl glutarate	12.55	3.54 (0.98)	2.73 (0.59)	2.02 (0.59)	5.47 (1.16)

[a] Parts per million (ppm) from capillary of TMS. [b] Chemical shift differences between protonated and unprotonated esters are in parentheses. [c] At −90°.

(through charge–charge repulsion) dispositive transition state, which leads to cleavage



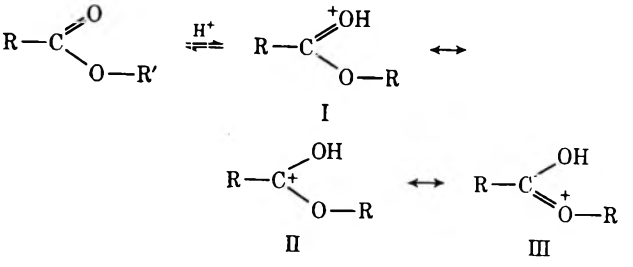
The possibility of diprotolytic cleavage is at the present time speculative as there has been no direct observation of any ether-oxygen protonated ester. Carbonyl oxygen protonated forms are highly stable and show little tendency to undergo intermolecular proton exchange. We are continuing our studies in the hope to clarify the possibility raised.

Diprotonated Dicarboxylic Acid Esters.—The protonation of dicarboxylic acids in superacid media has been studied by Olah and White.[28] It was shown by peak area integration of the pmr spectra of malonic, succinic, and glutaric acids in FSO_3H–SbF_5 that these acids existed as diprotonated species. It was not possible to decide, by the same method, if oxalic acid was also diprotonated, although the large deshielding of the oxygen protons (δ 15.70) suggested that this was the case.

We have studied by pmr and cmr spectroscopy the related problem of the extent of protonation of diesters in superacid systems at low temperatures. The diethyl esters of dicarboxylic acids gave well-resolved pmr spectra in FSO_3H–SbF_5 solution, diluted with SO_2. Chemical shift data are summarized in Table VI. Peak area integration of the spectra indicated that diethyl succinate and glutarate exist as diprotonated species at −60°. To observe the oxygen proton signals in protonated diethyl malonate it was necessary to record the spectrum at −90°, at which temperature the C–H protons were considerably broadened and a broad singlet was observed at δ 14.6. It was then possible by integration to show that this ester was diprotonated.

In principle, it should be possible using the same method to determine the extent of protonation in diethyl oxalate. This is not possible for oxalic acid because there are no other proton signals in the molecule, to compare with the oxygen proton signal. At −100°, the spectrum of diethyl oxalate in excess FSO_3H–SbF_5 indicated a very broad singlet at δ 11.6, implying that rapid proton exchange was still occurring between solvent and ester. Lowering the temperature did not slow the exchange rate sufficiently to observe a separate protonated ester signal. The changes in the methyl and methylene proton shifts, however, on protonation of diethyl oxalate are as large as those in the higher homologs, and, therefore, it seems that this ester, too, is diprotonated. For confirmation we have recorded the proton decoupled cmr spectrum of diethyl oxalate in FSO_3H–SbF_5 at −60°. The cmr spectra of protonated diethyl malonate, succinate, and glutarate, together with those of their parent compounds, have also been recorded; the results have been included in Tables I and II. The ^{13}C chemical shift data for the above esters, which are known to be diprotonated in FSO_3H–SbF_5, can be applied to the data for diethyl oxalate in order to determine its degree of protonation. Such a comparison of carbon shifts is more meaningful than for proton shifts, because of the lesser relative importance in the former case of field effects, and the greater sensitivity of the carbon shift to small structural changes within a molecule. The changes in the carbon shifts, on ester protonation, should be more a reflection of changes in the amount of charge located at a particular atom or on an adjacent oxygen or carbon atom than of solvent, field, or magnetic anisotropic effects.

It will be assumed in the following discussion that protonation of diesters in FSO_3H–SbF_5 occurs only on the acyl oxygen atom.[11] The equilibrium between an ester and its protonated form can be represented as

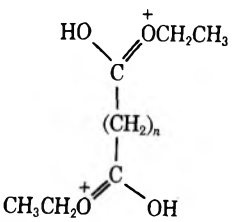


In excess HSO_3F–SbF_5, this equilibrium lies far to the right, and the carbonyl carbon and alkyl oxygen carbon resonances are deshielded 20 and 16 ppm, respectively, from their values in the unprotonated esters. In weaker acids, or where less than a molar amount of FSO_3H–SbF_5 is present, these chemical shifts should be the weighted average of the cationic species and the ester form, with which it is in rapid equilibrium. This was found to be the case for the methylene carbon resonance, the carbonyl carbon resonance, and the methylene and carbonyl oxygen proton resonances of ethyl formate in SO_2 at −60°, in the presence of less than molar amounts of FSO_3H–SbF_5. It should, therefore, be possible to use these chemical shifts to calculate the equilibrium position for a dicarboxylic acid ester in a superacid. For example, a mixture of equal numbers of monoprotonated diester and diprotonated diester species, in rapid equilibrium with each other, should have a carbonyl carbon resonance which is deshielded from the corresponding resonance in the unprotonated species by approximately three-quarters the amount observed in a protonated

(28) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, **89**, 4752 (1967).

monoester. This assumes that the relative contribution of resonance forms I, II, and III is the same in a protonated diester as it is in a protonated monoester. If the ester groups are separated by a sufficient number of methylene carbons, this should be true; otherwise the relative contributions of I and III may increase, because of the larger charge separation in these forms. The relevant figures to be considered in a discussion of the data in Table V, is, therefore, the sum of the change, on protonation, of the carbonyl carbon resonance ($\Delta\delta_{^{13}C=O}$) and the methylene carbon resonance ($\Delta\delta_{O-^{13}CH_2}$). These values are shown in the last column of this table.

The value of $\Delta\delta_{^{13}C=O} + \Delta\delta_{O-^{13}CH_2}$ for diethyl oxalate is almost as large as it is for the other diesters and ethyl formate. Assuming that the changes in the carbon shifts in diethyl oxalate are predominantly a result of localized charge effects and not of field or solvent effects arising from the close proximity of the two charged ester groups, these results indicate that diethyl oxalate in FSO_3H–SbF_5, at $-65°$, exists primarily as the diprotonated species. The larger $\Delta\delta_{O-^{13}CH_2}$ for protonated diethyl oxalate, compared with the corresponding values in the other protonated diesters, suggests that resonance form IV (analog of III) may be a more important con-



IV

tributor for this ester ($n = 0$) than for the other diesters ($n = 1, 2, 3$). The slightly smaller value of $\Delta\delta_{^{13}C=O} + \Delta\delta_{O-^{13}CH_2}$ for protonated diethyl oxalate may indicate a larger amount of equilibrating monoprotonated ester than is the case from the other protonated diesters, or it may be a result of solvent and field effects.

Experimental Section

Materials.—All esters were either commercially available materials or were prepared by standard literature methods and purified by distillation.

Preparation of Protonated Esters.—A sample of a protonated ester was prepared by adding the ester (0.5 ml) to a stirred solution of 1:1 *M* FSO_3H–SbF_5 (1.5 ml) in an equal volume of SO_2 at $-76°$. Samples prepared in this manner gave spectra which showed no appreciable chemical shift differences with temperature or small concentration variations. The acid was always in excess as indicated by an acid peak at about δ 10.9 in the pmr spectrum. The cmr spectrum of a protonated ester was only recorded if its pmr spectrum was identical with the spectrum reported in the literature.[11] For esters previously not reported, the structure of the protonated form could be established from the pmr spectral data (chemical shifts, multiplicity patterns, and peak area integration). After obtaining the cmr spectrum of a protonated ester, the sample was again checked by pmr spectroscopy to determine if any decomposition had occurred. Only the esters of secondary alcohols showed any observable decomposition (10–20%), cleaving by an $A_{AL}1$ mechanism to give protonated acids and stable tertiary carbenium ions.[11] No attempt to record the cmr spectra of protonated tertiary alkyl esters, such as *tert*-butyl acetate, as it is known that esters of tertiary alcohols cleave so rapidly, even at $-80°$, that only the protonated acid and the tertiary carbenium ion can be observed.

Nmr Spectroscopy.—Pmr spectra were obtained on a Varian Associates Model A-56/60-A spectrometer equipped with a variable temperature probe.

Cmr spectra were obtained on a Varian Associates Model HA-100 spectrometer equipped with a FT-100 Fourier transform accessory (V-4357 pulsing and control unit), a broad-band proton decoupler (V-3512), and a variable temperature probe. A pulsed frequency of 25.14 MHz was derived from a gated power amplifier capable of putting out approximately 80 W into the transmitter coils. The pulse width used was 30 μsec, and the pulse interval, 2 sec. The available computer memory (4000 imput channels) and the need to provide multichannel excitation over the region of interest (sweep width 6500 Hz) limited the data acquisition time to 0.3 sec.

The free induction signal derived after each pulse is digitized and accumulated in a Varian 620/i computer (8K). Approximately 3000–4000 accumulations were made to obtain each spectrum. Field/frequency regulation was maintained by a homonuclear internal lock system. The lock used was the proton decoupled ^{13}C resonance of a 30% ^{13}C-labeled methyl iodide sample contained in a precision coaxially spaced capillary (o.d. *ca.* 0.2 and 0.4 mm) inserted in the sample nmr tube (5-mm o.d.).

Fourier transformation of the accumulated free-induction signal gave the frequency spectrum[13,29,30] from which was measured the chemical shift of each signal, relative to the reference methyl iodide signal. All the chemical shifts reported here have been corrected to a carbon disulfide reference by the relationship

$$\delta_{CS_2} = 212.2 - a\delta T - \delta_{CH_3I}$$

where δ_{CS_2} and δ_{CH_3I} are the chemical shifts in parts per million of a particular signal, from carbon disulfide and methyl iodide, respectively. The term $a\delta T$ allows for the observed temperature variation in the chemical shift of internal carbon disulfide with respect to that of external methyl iodide, and δT is the difference between the normal probe temperature (30–35°) and the temperature at which a spectrum is recorded. A plot of sample temperature *vs.* the ^{13}C chemical shift difference between external methyl iodide and carbon disulfide is linear with a slope of $a = 0.029 \pm 0.002$ ppm/°C. The slope was found to almost identical for several carbon disulfide–cosolvent systems; so the above expression is most likely valid for the superacid solvent systems employed in this study. The value 212.2, in the above expression, is the experimentally measured chemical shift difference between carbon disulfide and external methyl iodide, at normal probe temperature.

Acknowledgment.—Support of our work by the National Institutes of Health is gratefully acknowledged.

(29) R. Ernst, "Advances in Magnetic Resonance," Vol. 2, Academic Press, New York, N. Y., 1966, p 74 ff.

(30) A. Abragam, "Principles of Nuclear Magnetism," Oxford University Press, London, 1961, p 114.

Photolysis of 2-Keto-2,3-dihydrobenzofurans, o-Hydroxystyrenes, and 1-(o-Hydroxyphenyl)-1,5-hexadienes

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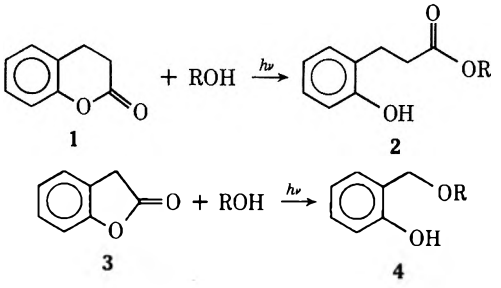
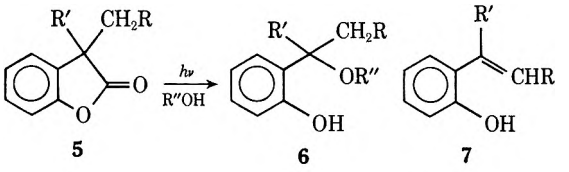
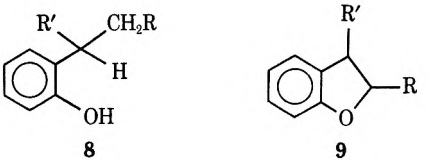
Received December 23, 1971

In continuation of earlier work in which it had been demonstrated that the photolysis of a methanol solution of 2-keto-2,3-dihydrobenzofuran yields methyl 2-hydroxybenzyl ether, the photolysis of several 3,3-disubstituted 2-keto-2,3-dihydrobenzofurans (**5**) has been studied. It has been found that, in addition to the ethers (**6**), the product mixture may also include olefins (**7**), reduction products (**8**), and dihydrobenzofurans (**9**) and that its composition is a function of the substituents at the C-3 position of **5**, the solvent, the concentration, and the incidence of secondary photolysis processes. To explain the results it is suggested that (a) the initially formed product from **5** is a quinonemethide, (b) the quinonemethide can react with alcohol, *via* a Michael addition, to form the ether and/or undergo intramolecular hydrogen transfer to form the olefin, (c) the olefin upon excitation can revert to the quinonemethide, cyclize to the dihydrobenzofuran, and/or react with the solvent to form reduction product. In support of this hypothesis it has been shown that (a) photolyses of the olefin (**7**) in methanol solution leads to product mixtures similar to those obtained from the 2-keto-2,3-dihydrobenzofurans and (b) photolyses of 2-keto-3-trideuteriomethyl-3-phenylbenzofuran (**5e**) and 1-phenyl-1-(*o*-hydroxyphenyl)-2,2-dideuterioethylene (**7e**) yield products in which some deuterium exchange has occurred. A chemical application of the Förster–Weller effect was sought in the photolysis of three 1-(*o*-hydroxyphenyl)-1,5-hexadienes which, it was hoped, would yield the cyclopentyl or cyclohexyl compounds **14–16**. Instead, however, the products parallel those obtained from the photolysis of the analogous *o*-hydroxystyrenes.

Whereas photolyses of alcohol solutions of 3,4-dihydrocoumarin (**1**) yield alkyl β-(2-hydroxyphenyl)-propionates (**2**), similar treatment of 2-keto-2,3-dihydrobenzofuran (**3**) yields 2-hydroxybenzyl ethers (**4**).[1] Further study has now revealed that ethers are







a, R = H; R′ = CH_3
b, R = CH_3; R′ = C_2H_5
c, R = H; R′ = C_6H_5
d, R = CH_3; R′ = C_6H_5
e, CH_2R = CD_3; R′ = C_6H_5

but one of several products that can be formed in the latter case and that the outcome can be affected by the substituents at C-3 of the 2-keto-2,3-dihydrobenzofuran, the solvent, the concentration, and the extent to which secondary photolysis takes place. The present paper is concerned with a discussion of these several factors.

Photolysis Products from 3,3-Disubstitued 2,3-Dihydrobenzofurans.—Employing alcohols and hydrocarbons as solvents, irradiations were carried out with 2-keto-2,3-dihydrobenzofurans substituted at C-3 with two methyl groups (**5a**), two ethyl groups (**5b**), one methyl and one phenyl group (**5c**), and one ethyl and one phenyl group (**5d**). The products obtained from these photolyses include ethers (**6**), olefins (**7**), reduction compounds (**8**), and dihydrobenzofurans (**9**), as shown in Table I. Inspection of this table reveals that (a) compounds **5a**, **5c**, and **5d** all yield ethers (**6**) as a major product in methanol solution, whereas compound **5b** yields the olefin (**7**), (b) the extent of ether formation in all cases diminishes as the solvent is changed from methanol to ethanol to 2-propanol, (c) the ratio of ether to reduction compound produced from **5c** decreases as the concentration of **5c** decreases, and (d) the olefins (**7**), formed at least in trace amounts in almost all cases, become the exclusive products in hydrocarbon solvents.

Photolysis Products from *o*-Hydroxystyrenes.—The substituted styrenes **7a–d**, which are the exclusive products from the photolysis of **5a–d** in hydrocarbon solvents, are also formed when the photolyses are carried out in alcohol solution. This suggests the possibility of a precursor role for the olefin with respect to the ether; to test this hypothesis methanol solutions of the olefins **7a–d** were irradiated. The results from these experiments, listed in Table II, show that (a) olefins **7a**, **7c**, and **7d** yield product mixtures qualitatively identical with and quantitatively similar to those obtained by photolysis of **5a**, **5c**, and **5d** in methanol; (b) olefin **7b** undergoes no change except a cis–trans isomerization; and (c) the ratio of ether to reduction produced from **7c** decreases as the concentration of **7c** decreases.

The photoinduced alcoholsis of 3,4-dihydrocoumarin to alkyl β-(2-hydroxyphenyl)propionates has been rationalized in terms of a spiro diketone intermediate[1] and a ketene intermediate,[2] the latter having been shown

(1) C. D. Gutsche and B. A. M. Oude-Alink, *J. Amer. Chem. Soc.*, **90**, 5855 (1968).

(2) D. A. Plank, PhD. Thesis, Purdue University, 1966.

TABLE I

PHOTOLYSIS OF 3,3-DISUBSTITUTED 2-KETO-2,3-DIHYDROBENZOFURANS

Starting compd				Concn,		Appara-	Product, % yield				
	R	R′	Solvent	mmol/l.	Time, hr	tus[a]	5	6	7	8	9
5a	H	CH_3	MeOH	96.0	9	A	47	38	8	7	
			2-PrOH	37.7	2.5	A	53.5	6.5	40	3.5	
			Pentane	12.3	1	A	27.5		72.5		
5b	CH_3	C_2H_5	MeOH	97.5	13	A	56.5	4.5	39		
			2-PrOH	27.2	4	A	33		47		
			Pentane	18.1	1	A	57		43		
5c	H	C_6H_5	MeOH	25.0	18	B	11	68.5	4.1	13.7	
				12.0	18	B		57.6	4.6	21.2	
				7.9	9	B		21.4	24.1	18.8	
				4.1	18	B		32.8		36.2	
			EtOH	25.0	18	B	17	50	9	14.5	
			2-PrOH	25.0	18	B	25	29	18	9	
			Hexane	25.0	18	B	72		10		
5d	CH_3	C_6H_5	MeOH	25.0	18	B	33	30	13		27
			EtOH	25.0	18	B	36	28	10.5		26
			2-PrOH	25.0	18	B	47	18	9		22
			Hexane	25.0	18	B	69		28		

[a] A, 300-ml quartz immersion well 450-W Hg lamp; B, 600-ml Rayonet Model RPR-100 reactor with Hg lamps.

TABLE II

PHOTOLYSIS OF *o*-HYDROXYSTYRENES IN METHANOL SOLUTION

Starting compd						Product, % yield			
	R	R′	Concn, mmol/l.	Time, hr	Apparatus[a]	7	6	8	9
	H	H	52.8	18	B	12.5	56.3		
7a	H	CH_3	93.3	18	B	9.9	81.8	4.3	
7b	CH_3	C_2H_5	7.5	1.5	A	92			
7c	H	C_6H_5	56.6	18	B	3	93	4	
			27.3	18	B	6.8	57	15	
			19.3	18	B	4.6	50.6	18.4	
			14.3	18	B		51.2	24.0	
			8.84	18	B		40.7	32.6	
			5.48	18	B		33.2	36.6	
			3.73	0.33	A		28.5	42.5	
			2.82	18	B		17.0	43.7	
7d	CH_3	C_6H_5	16.4	18	B	6.2	35.9		47.6
			4.02	0.25	A		42.2		57.8

[a] A, 300-ml quartz immersion well with 450-W Hg lamp; B, 600-ml Rayonet Model RPR-100 reactor with Hg lamps.

quite conclusively, on the basis of low-temperature spectral observations and deuterium incorporation experiments, to account for at least part of the product.[3,4] Either of these intermediates would be more difficult to generate from 2-keto-2,3-dihydrobenzofurans, *i.e.*, the spiro diketone because of increased ring strain and the ketene because of a less accessible hydrogen for intramolecular transfer. Rather than following either of these pathways, therefore, the photoexcited 2-keto-2,3-dihydrobenzofuran loses carbon monoxide to yield a species which can be formulated as an *o*-quinonemethide.[5]

o-Quinonemethides react rapidly with nucleophiles, but alternative pathways may be followed if nucleophiles are not present. For example, the quinonemethides **10a–d** can rearrange, by intramolecular hydrogen transfer, to the corresponding *o*-hydroxystyrenes **7a–d**. This process, which is the exclusive one in hydrocarbon solvents, may also take place in protic solvents, and the olefins **7a–d** have been shown to be possible progenitors of the ethers **6a–d**. The immediate precursor to the ethers, however, is considered to be the *o*-quinonemethide (whether it be formed from the 2-keto-2,3-dihydrobenzofurans or from the *o*-hydroxystyrenes), which reacts with alcohol *via* nucleophilic attack (Michael addition) at the benzyl carbon atom.[6] The diminishing yield of ether with increasing size of the nucleophile (methanol to ethanol to 2-propanol) is in accord with the known sensitivity of Michael addi-

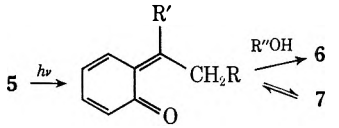
(3) O. H. Chapman and C. L. McIntosh, *J. Amer. Chem. Soc.*, **91**, 4309 (1969).

(4) On the basis of *apparent* nonincorporation of deuterium into **2** when a sample of **1** was irradiated in CH_3OH solution, the present authors favored the spiro diketone mechanism.[1] More recent work by Chapman and McIntosh,[3] however, has shown that a significant amount of deuterium *is* incorporated into **2**. The difference between these two sets of experiments is in the method of product assay that was employed, *viz.*, nmr in our case and mass spectra by Chapman and McIntosh. A recheck of our data showed that, although the purified sample of methyl β-(2-hydroxyphenyl)-propionate appeared to contain no carbon-bound deuterium, as indicated by a ratio of 1.0 for the CH_2/ArH resonance in the nmr, the crude photolysis product showed a CH_2/ArH ratio of only 0.89, corresponding to a 45% incorporation of deuterium into a methylene group. Repetition of the experiment produced a sample of the ester which has been shown by mass spectral analysis to contain 31% $C_{10}H_{12}O_3$, 48% $C_{12}H_{11}DO_3$, and 21% $C_{12}H_{10}D_2O_3$ (as C-bound deuterium), in accord with the findings of Chapman and McIntosh.

(5) Using low-temperature methods [*cf.* O. L. Chapman and J. D. Lassila, *J. Amer. Chem. Soc.*, **90**, 2449 (1968); L. L. Barber, O. L. Chapman, and J. D. Lassila, *ibid.*, **90**, 5933 (1968); **91**, 531 (1969)], Chapman and coworkers have detected *o*-quinonemethide as a product from the photolysis of **3** (O. L. Chapman, private communication).

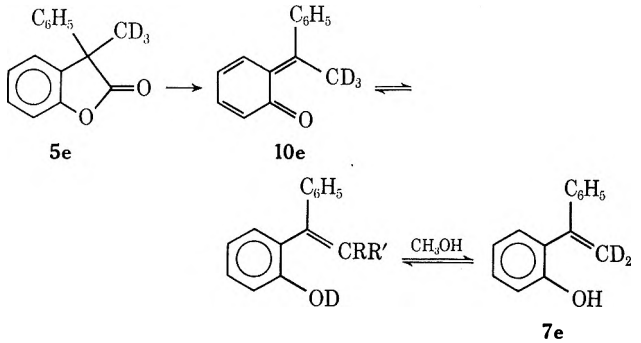
(6) A. B. Turner, *Quart. Rev.*, **18**, 347 (1964).

tions to steric factors;[7] the higher yield of ether from **7c** and **7d** is in accord with the stabilization of the quinonemethide by the phenyl group at C-3; the failure of **5b** to yield ether and its propensity to simply undergo cis–trans isomerization, although surprising, can be attributed to the lack of resonance stabilization of the quinonemethide (*i.e.*, no phenyl group at C-3) and to the increased steric hindrance arising from two ethyl groups at C-3.



10

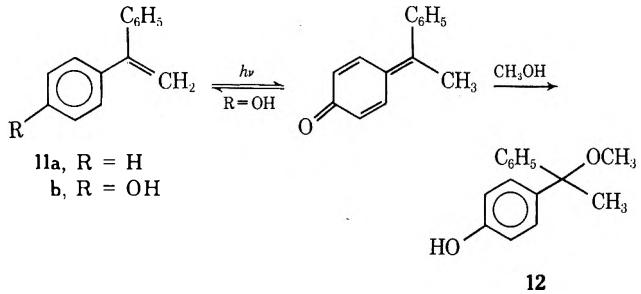
Experiments with deuterium-labeled compounds suggest that part of the ether may be formed directly from the 2-keto-2,3-dihydrobenzofuran, presumably *via* the quinonemethide, and that at least part must be formed *via* cycling through the olefin. Starting with the trideuterio compound **5e**, ether containing 2.65 C-bound deuterium atoms was obtained; starting with olefin containing 1.78 deuterium atoms in the vinyl positions, ether containing 1.54 C-bound deuterium atoms was obtained. If the ether from **5e** had its origin only from directly formed **10e**, the deuterium content should be



5e 10e 7e

R, R′ = D
R = D; R′ = H
R, R′ = H

3.00 atoms; if, on the other hand, cycling between the *o*-quinonemethide and the olefin precedes ether formation, the deuterium content should fall below 3.00 atoms and could approach zero. The results indicate that such cycling must take place, although in the absence of quantitative data for the rate of interconversion of *o*-quinonemethide to olefin and the rate of hydrogen transfer from olefin to methanol an accurate assessment of the fraction of ether formed in this manner cannot be made.



11a, R = H
b, R = OH

12

(7) E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. React.*, **10**, 179 (1959).

The necessity that a phenolic group be present if the ether is to be a product is shown by the failure of 1,1-diphenylethylene (**11a**) to undergo any reaction whatsoever under the conditions that convert its hydroxylated analog **7c** to the ether **6c**. It is not essential, however, that the hydroxyl function be in the ortho position, for 1-phenyl-1-*p*-hydroxyphenylethylene (**11b**) also forms an ether (**12**), although at a considerably slower rate. A quinonemethide intermediate can, of course, be invoked in this case also,[8] but an intermolecular rather than an intramolecular pathway would seem to be necessary for its formation.

A working hypothesis for rationalizing these four different reaction pathways asserts, albeit with little hard evidence, that (a) the ether arises from the *o*-quinonemethide, and the reduction product and benzofuran arise from the *o*-hydroxystyrene; (b) the formation of *o*-quinonemethide from the *o*-hydroxystyrene is the result of an intramolecular hydrogen transfer from the phenolic hydroxyl group to the β carbon of the styrene, and the reduction product and benzofuran are the result of intramolecular hydrogen transfer from the phenolic hydroxyl group to the α carbon of the styrene; and (c) the partitioning of hydrogen between the α and β positions is sensitive to structure, conformation, solvent, and concentration. The chromophore in the *o*-hydroxystyrenes that is responsible for initiating these events is uncertain. The studies of Förster and Weller[9] showing enhanced acidity of phenols in the electronically excited state, along with the recently reported photochemical conversions of 2-allylphenols to 2,3-dihydrobenzofurans,[10] support the possibility that the phenolic moiety is the essential chromophore and that the hydrogen is transferred as a proton. That photochemical additions, including reductions, can involve ionic intermediates has been demonstrated by the work of Marshall[11] and Kropp.[12] Activation *via* the styrene chromophore and the involvement of radicals cannot be discounted, however; reduction products from the somewhat analogous system, spiro[2.5]octa-4,7-dien-6-one, have, for instance, been explained in terms of radical intermediates.[13] It should be emphasized that these proposals are meant to be nothing more than tentative working hypotheses. Other schemes, intermediates, and mechanistic pathways can, of course, be envisaged, and additional experiments clearly are required to substantiate or refute the ideas embodied in the present scheme. See Scheme I.

Photolysis Products from 1-(*o*-Hydroxyphenyl)-1,5-hexadienes.—In continuation of a quest for a chemical application of the Förster–Weller effect,[9] three 1-(*o*-hydroxyphenyl)-1,5-hexadienes (**13**) have been prepared and irradiated in methanol solution in the hope that the cyclization products **14**–**16** might be observed. This expectation was not realized, however, and the

(8) The irradiative conversion of 1-(*p*-hydroxyphenyl)propene to the corresponding *p*-quinonemethide has been demonstrated by means of flash photolysis by G. Leary, *Chem. Commun.*, 688 (1971).

(9) T. Förster, *Z. Elektrochem.*, **54**, 42 (1950); A. Weller in "Progress in Reaction Kinetics," Vol. 1, G. Porter, Ed., Pergamon Press, Oxford, 1961, p 187; *cf.* E. L. Wehry and L. B. Rogers, *J. Amer. Chem. Soc.*, **87**, 4234 (1965), for a list of other pertinent references for this phenomenon.

(10) W. H. Horspool and P. L. Pauson, *Chem. Commun.*, **4**, 195 (1967); G. Frater and H. Schmid, *Helv. Chim. Acta*, **50**, 255 (1967).

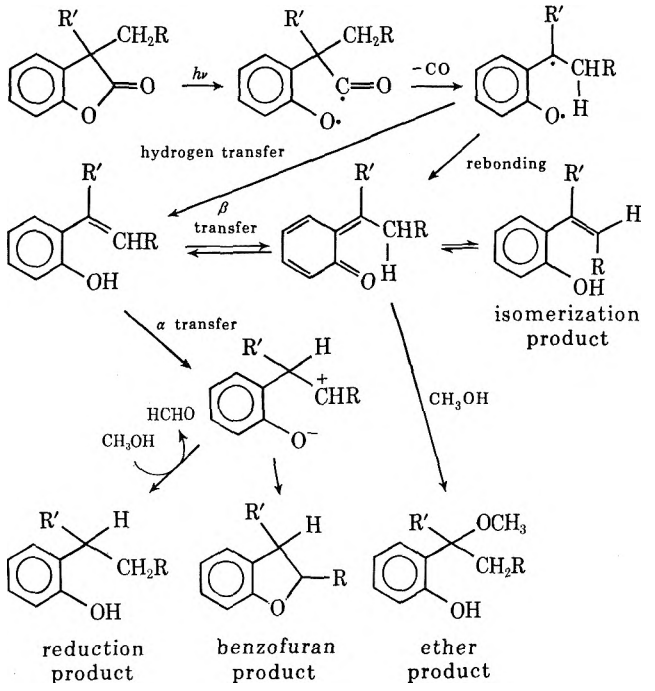
(11) J. A. Marshall, *Accounts Chem. Res.*, **2**, 33 (1969).

(12) P. J. Kropp and H. J. Krauss, *J. Amer. Chem. Soc.*, **91**, 7466 (1969).

(13) D. I. Schuster and C. J. Polowczyk, *J. Amer. Chem. Soc.*, **88**, 1722 (1966).

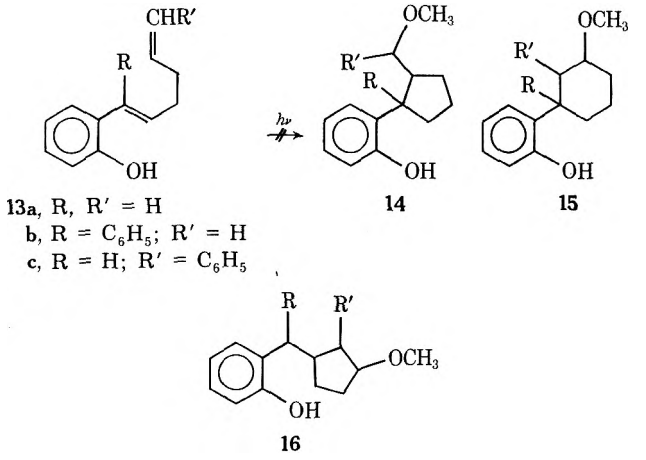
SCHEME I

PHOTOLYSIS PATHWAYS FOR 2-KETO-2,3-DIHYDROBENZOFURANS



products proved to be similar to those obtained from the analogous *o*-hydroxystyrenes.

Compounds **13a** and **13b** were prepared by the action of 2 molar equiv of the appropriate Grignard reagent

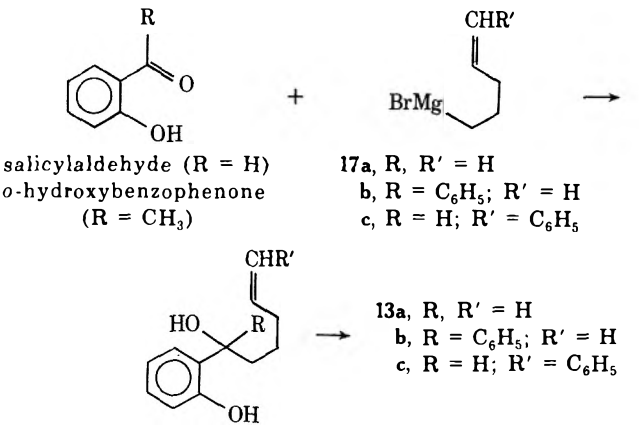


13a, R, R′ = H
b, R = C_6H_5; R′ = H
c, R = H; R′ = C_6H_5

14 **15**

16

on salicylaldehyde and *o*-hydroxybenzophenone, respectively, followed by dehydration of the initially formed alcohol. In the case of salicylaldehyde and 1-pentenylmagnesium bromide, the alcohol **17a** was isolable and, in fact, required a vapor-phase pyrolysis to effect conversion to the diene **13a**. With *o*-hydroxybenzophenone and 1-pentenylmagnesium bromide, on the other hand, the alcohol **17b** was not isolated, and the diene **13b** was obtained directly from the acidified Grignard mixture. The action of 1-phenyl-1-pentenylmagnesium bromide on salicylaldehyde yielded the alcohol **17c**, but attempts to dehydrate it to the diene **13c** furnished a compound which is thought to be 4-phenyl-1,2,3,3a,4,9b-hexahydrocyclopenta[*c*][1]benzopyran (**19**). The elemental analysis and nmr spectrum of the compound are compatible with this formulation, and the action of sodium and pyridine cleaves **19** to the

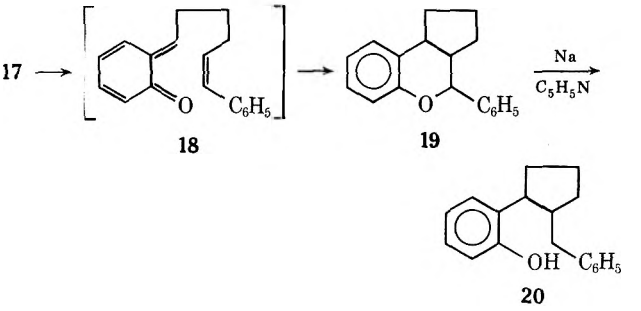


salicylaldehyde (R = H)
o-hydroxybenzophenone (R = CH_3)

17a, R, R′ = H
b, R = C_6H_5; R′ = H
c, R = H; R′ = C_6H_5

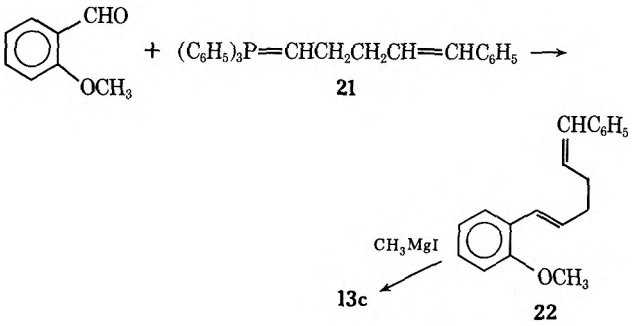
13a, R, R′ = H
b, R = C_6H_5; R′ = H
c, R = H; R′ = C_6H_5

phenol **20**. A plausible mechanism for the formation of **19** from **17** involves a prior conversion to the quinonemethide **18** followed by an intramolecular Diels–Alder



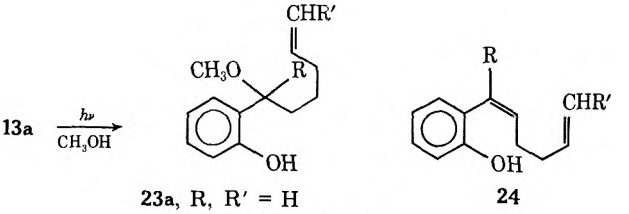
18 **19** **20**

reaction. Other routes to the synthesis of **13c** were investigated, and the one that proved to be successful involves the formation of the diene **22** (by the action of the Wittig reagent **21** on 2-methoxybenzaldehyde) followed by demethylation to the desired diene.



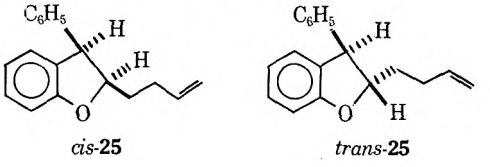
21 **22**

Irradiation of a 10^{-2} *M* solution of **13a** in methanol yielded a mixture which was shown to contain some of the ether **23a** along with larger amounts of the starting material **13a** and its cis isomer **24**. Aliquots removed



23a, R, R′ = H
b, R = C_6H_5; R′ = H
c, R = H; R′ = C_6H_5

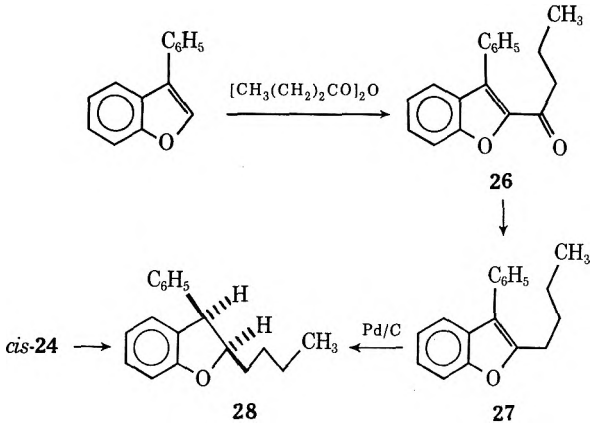
24



cis-**25** *trans*-**25**

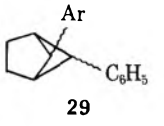
from the photolysis mixture at various times showed that the cis:trans ratio increases to a maximum of 82:18 after 2 hr and then recedes slightly to *ca.* 75:25 after 4 hr. The decrease is attributed to the formation of more **23a** in the longer photolysis and its subsequent thermal decomposition to **13a** during the glc analysis of the product. Analogous results have been noted in the *o*-hydroxystyrene series, where *o*-hydroxystyrene yields the ether as the major product, but 3-(*o*-hydroxyphenyl)-2-butene undergoes cis–trans isomerization. Irradiation of **13a** in cyclohexane rather than methanol solution results in cis–trans isomerization and polymerization.

Irradiation of a 10^{-2} *M* solution of **13b** in methanol yields a mixture which contains the cis and trans isomers of 2-(3-butenyl)-3-phenyldihydrobenzofuran (**25**) as the major components along with a small amount of the ether **23b**. The isomers of **25** were separated by column chromatography, and the assignments of stereochemistry[14] were made on the basis of a comparison with the cis-dihydro compound **28**, which was prepared by the conversion of 3-phenylbenzofuran to 2-butanoyl-3-phenylbenzofuran (**26**), Huang-Minlon reduction of **26** to 2-butyl-3-phenylbenzofuran (**27**), and catalytic reduction of **27** to *cis*-2-butyl-3-phenyldihydrobenzofuran (**28**). The formation of **25** from **13b** finds its



analog in the photolysis of 1-(*o*-hydroxyphenyl)-1-phenyl-1-propene (**7d**), where the dihydrobenzofuran is the sole product.

In the photolysis of **13a** and **13b** there is no evidence for any involvement of the terminal double bond, the products being analogous to those observed in the corresponding *o*-hydroxystyrene series. That it was, perhaps, naive to have expected such involvement is indicated by attempts to induce an acid-catalyzed cyclization of **13b**. The action of hydrobromic acid–acetic acid as well as that of refluxing methanol containing concentrated sulfuric acid on **13b** were both without effect, and aqueous methanolic sulfuric acid led to decomposition products. In the thought that a phenyl group attached to the terminal double bond might increase the possibility of interaction with the conjugated double bond, **13c** was next investigated. Irradiation of a 10^{-2} *M* solution of **13c** in methanol resulted in the disappearance of starting compound and the formation of a mixture containing *ca.* 40% of volatile material. The ir spectrum of the volatile product showed a strong hydroxyl absorption, and the nmr spectrum indicated the absence of vinyl protons, the absence of methoxyl protons, and the presence of a pair of benzylic protons. These data are compatible with structure **29**, which would be the result of an intra-



29

molecular cycloaddition of the two styrene moieties.[15] Further efforts to substantiate this structure were not undertaken, however, for a glc analysis of the silyl derivative of the crude product indicated that at least four components were present, none of which appeared to be compounds of the type **14**–**16**.

Experimental Section[16]

Synthesis of 2-Keto-2,3-dihydrobenzofurans. 2-Keto-2,3-dihydrobenzofuran (3).—Following published procedures, *o*-methoxybenzaldehyde was converted to its cyanohydrin[17] in 72% yield, the cyanohydrin was hydrolyzed to *o*-hydroxyphenylacetic acid in 57% yield,[18] and the acid was lactonized to afford **3** in 85% yield as a colorless solid: uv max (95% EtOH) 271 nm (ε 1225) and 277 (1210); ir (liquid) 1800 and 1775 cm^{-1} (C=O); nmr (CCl_4) δ 4.54 (s, 2, $ArCH_2$) and 6.80–7.40 ppm (m, 4, ArH).

2-Keto-3,3-dimethyl-2,3-dihydrobenzofuran (5a).—A solution of 30 g of 2-keto-2,3-dihydrobenzofuran in 50 ml of dimethylformamide was added, dropwise over a period of 30 min, to a stirred and cooled suspension of 19 g of sodium hydride in 125 ml of dimethylformamide. Stirring and cooling were continued until the evolution of hydrogen ceased (*ca.* 20 min), and 150 g of methyl iodide was then added. The reaction mixture was stirred for 20 hr at room temperature and then processed in the usual fashion to yield 24 g of a colorless oil, bp 79–82° (0.08 mm), which was shown by glc analysis to contain product and starting material in an 85:15 ratio. Distillation through a spinning band column achieved only partial separation, whereas passage through a glc column afforded 16.0 g (44%) of pure material: bp 43° (0.05 mm); uv max (95% EtOH) 270 nm (ε

(14) The magnitude of the H_2–H_3 coupling constant provides an uncertain guide for the specification of the stereochemistry in these compounds. In the case of 2,3-dialkyl-2,3-dihydrobenzofuran [E. C. Hayward, D. S. Tarbell, and L. D. Colebrook, *J. Org. Chem.*, **33**, 399 (1968)], 2-phenyl-3-hydroxy-2,3-dihydrobenzofuran [S. P. Pappas, R. D. Zehr, and J. E. Alexander, *J. Heterocycl. Chem.*, **7**, 1215 (1970)], and 2-methyl-3-hydroxy-2,3-dihydrobenzofuran [M. P. Mertes and L. J. Powers, *Chem. Commun.*, 620 (1970)], J_{23} is greater for the cis isomer than for the trans isomer. In the case of 2-isopropyl-3-hydroxy-2,3-dihydrobenzofuran [L. H. Zalkow and M. Ghosal, *Chem. Commun.*, 922 (1967)] and 2-methyl-3-acetoxy-5-nitro- (and 7-nitro-) 2,3-dihydrobenzofuran [M. P. Mertes, L. J. Powers, and E. Shefter, *J. Org. Chem.*, **36**, 1805 (1971)], however, J_{23} is greater for the trans than for the cis isomer. The third alternative is observed in 2-phenyl-3-methyl-2,3-dihydrobenzofuran [M. Gregson, W. D. Ollis, R. T. Redman, and I. O. Sutherland, *Chem. Commun.*, 1394 (1968)] where J_{23} is the same for the cis and trans isomers, in close correspondence with the observations in the present instance where J_{23} for the cis isomer is 7.9 Hz and that for the trans isomer is 7.6 Hz.

(15) R. Srinivasan, *J. Phys. Chem.*, **67**, 1367 (1963); *J. Amer. Chem. Soc.*, **85**, 819 (1963); K. J. Crowley, *Proc. Chem. Soc.*, 17 (1964); *J. Amer. Chem. Soc.*, **86**, 5692 (1964); J. K. Crandall and C. F. Mayer, *J. Org. Chem.*, **35**, 3049 (1970).

(16) Melting points and boiling points are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Infracord spectrometer; the ultraviolet spectra were recorded on Cary Model 11 and Model 14 spectrometers; the nuclear magnetic resonance spectra were recorded on Varian A-60A instruments, and the resonances are stated in parts per million downfield shift from tetramethylsilane used as an internal reference. Glc analyses were performed on units containing thermistor detectors and using the following columns: column 1, a 0.25 in. × 16 ft column packed with 15% w/w neopentylglycol sebacate polymer on 40–50 mesh type ABS Anakrom (a product of Analytical Engineering Laboratory, Inc., Hamden, Conn.); column 2, 0.25 in. × 6 ft column packed with 5% w/w Dow No. 710 silicone oil on a 40–50 mesh type ABS Anakrom. Microanalyses were performed by Mikroanalytisches Laboratorium, Vienna, Austria.

(17) Levine, T. E. Eble, and H. Fischbach, *J. Amer. Chem. Soc.*, **70**, 1930 (1948).

(18) S. Czaplicki, St. v. Kostanecki, and V. Lampe, *Chem. Ber.*, **42**, 827 (1909).

1225) and 276 (1160); ir (liquid) 1800 cm^{-1} (C=O); nmr (CCl_4) δ 1.47 (s, 6, CH_3) and 7.08–7.68 ppm (m, 4, ArH).

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.02; H, 6.61.

2-Keto-3,3-diethyl-2,3-dihydrobenzofuran (5b).—Following the procedure described above, 40.2 g of 2-keto-2,3-dihydrobenzofuran yielded 32 g (57%) of **5b** as a colorless oil: bp 68–70° (0.07 mm); uv max (95% EtOH) 270 nm (ϵ 1235) and 277 (1180); ir (liquid) 1800 cm^{-1} (C=O); nmr (CCl_4) δ 0.69 (t, 6, J = 7.3 Hz, CH_2CH_3), 1.94 (q, 2, J = 6.9 Hz, CH_2CH_3), 1.96 (q, 2, J = 7.7 Hz, CH_2CH_3), 7.08–7.68 ppm (m, 4, ArH).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.96; H, 7.56.

2-Keto-3-phenyl-2,3-dihydrobenzofuran.—Following a published procedure[19] a 114-g sample of (*R,S*)-mandelic acid was heated with 81.5 g of phenol and 225 ml of 73% sulfuric acid to yield, after two recrystallizations from 95% ethanol, 45 g (35%) of colorless needles: mp 117–118° (lit. mp 113–114°); uv (95% EtOH) 272 nm (ϵ 1515), 279 (1420), and 318 (200, arising from the enol form and absent when 1,2-dichloroethane is the solvent); ir (KBr) 1805 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4.86 (s, 1, ArCH) and 7.00–7.50 ppm (m, 9, ArH).

Anal. Calcd for $C_{14}H_{12}O_2$; C, 79.98; H, 4.79. Found: C, 80.05; H, 4.94.

2-Keto-3-methyl-3-phenyl-2,3-dihydrobenzofuran (5c).—A 15.75-g sample of 2-keto-3-phenyl-2,3-dihydrobenzofuran in 20 ml of dimethylformamide was added to a cooled and stirred mixture of 3.3 g of sodium hydride in 90 ml of dimethylformamide. After hydrogen evolution ceased (*ca.* 15 min), 13.8 g of methyl iodide was added, and the reaction mixture was stirred for 20 hr at room temperature. The product was obtained in the usual fashion and was distilled to yield 14.2 g (85%) of **5c** as a colorless, heavy oil: bp 130–135° (0.04 mm); uv mas (95% EtOH) 271 nm (ϵ 1360) and 277 (1240); ir (liquid) 1805 cm^{-1} (C=O); nmr (CCl_4) δ 1.82 (s, 3, CH_3) and 6.82–7.50 ppm (m, 9, ArH).

Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.29. Found: C, 80.61; H, 5.53.

2-Keto-3-trideuteriomethyl-3-phenyl-2,3-dihydrobenzofuran (5e).—Using trideuteriomethyl iodide in the procedure described above, **5e** was obtained as a colorless oil: uv max (95% EtOH) 271 nm (ϵ 1260) and 277 (1200); ir (liquid) 1800 cm^{-1} (C=O); nmr (CCl_4) δ 6.82–7.50 (m, 9, ArH).

2-Keto-3-ethyl-3-phenyl-2,3-dihydrobenzofuran (5d).—Following the procedure described above with ethyl bromide in place of methyl iodide, **5d** was obtained in 88% yield as colorless crystals: mp 69–70°; uv max (95% EtOH) 271 nm (ϵ 1550) and 278 (1395); ir (KBr) 1805 cm^{-1} (C=O); nmr (CCl_4) δ 0.75 (t, 3, J = 7 Hz, CH_2CH_3), 2.25 (q, 1, J = 7 Hz, CH_2CH_3), 2.33 (q, 1, J = 7 Hz, CH_2CH_3, 6.50–7.60 (m, 9, ArH).

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.60; H, 6.01.

Synthesis of o-Hydroxystyrenes. 2-Hydroxyphenylethylene was prepared by decarboxylation of *o*-hydroxycinnamic acid according to a published procedure[20] and obtained as a colorless oil: bp 92–95° (11 mm); nmr (CCl_4) δ 5.24 (doubled doublet, 1, J = 1.6 and 11 Hz, =CH_2), 5.68 (doubled doublet, 1, J = 1.6 and 17 Hz, =CH_2), 6.19 (s, 1, OH), 6.91 (doubled doublet, 1, J = 11 and 17 Hz, =CH) 6.50–7.65 ppm (m, 4, ArH); uv and ir identical with published data.[21]

2-(2-Hydroxyphenyl)propene (7a).—A 40-g sample of *o*-hydroxyacetophenone in 100 ml of dry ether was treated with 250 ml of a 3 *M* solution of methylmagnesium chloride in tetrahydrofuran. The carbinol was dehydrated by heating for 10 min at 180°, and the resulting product was twice distilled under reduced pressure to yield 35 g of **7a** as a colorless oil: bp 50–52° (0.7 mm); uv max (95% EtOH) 240 sh (ϵ 5000) and 282 (2460); ir (liquid) 3550 cm^{-1} (OH); nmr (CCl_4) δ 2.05 (s, 3, CH_3), 5.08 (broad d, 1, =CH_2), 5.22 (d, 1, =CH_2), 5.73 (s, 1, OH), and 6.50–7.30 ppm (m, 4, ArH).

Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.62; H, 7.75.

1-Phenyl-1-(2-hydroxyphenyl)ethene (7c).—Starting with 25 g of *o*-hydroxybenzophenone and following the procedure described above, 20 g of **7c** was obtained as a viscous oil: bp 102–103° (0.05 mm); uv max (95% EtOH) 281 nm (ϵ 3420); ir (liquid) 3600 cm^{-1} (OH); nmr (CCl_3) δ 6.02 (s, 1, OH), 5.32 (d, 1, =CH_2), 5.74 (d, 1, =CH_2), and 6.63–7.58 ppm (m, 9, ArH).

Anal. Calcd for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.68; H, 6.21.

1-Phenyl-1-(2-hydroxyphenyl)-2,2-dideuterioethene (7e).—A 6.0-g sample of **7c** was dissolved in 3.5 ml of methanol-d_1, the methanol was removed by distillation, and the residue was heated at 180–185° for 10 min in a stream of nitrogen. This process was repeated several times to yield a product, bp 101° mm), which was shown by nmr analysis to contain 1.78 deuterium atoms at the 2 position.

1-Phenyl-1-(2-hydroxyphenyl)propene (7d).—Starting with 25 g of *o*-hydroxybenzophenone and using ethylmagnesium bromide in the procedure described above, 15.5 g of **7d** was obtained as a colorless oil: bp 102–105° (0.05 mm); ir (liquid) 3600 cm^{-1} (OH); nmr (CCl_4) δ 1.60 (d, 2.1, CH_3 of *E* isomer), 1.77 (d, 0.9, CH_3 of *Z* isomer), 5.25 (s, 1.0, OH), 5.87 (q, 0.3, =C*H* of *Z* isomer), 6.26 (q, 0.7, =C*H* of *E* isomer), 6.50–7.50 ppm (m, 9, ArH). The nmr intensities indicate that the product is a mixture containing *ca.* 5 parts of the *E* isomer and 2 parts of the *Z* isomer. Confirmation of the structure was achieved by conversion to 2-methyl-3-dihydrobenzofuran (**9d**).

1-Phenyl-1-(4-hydroxyphenyl)ethene (11b) was prepared from *p*-hydroxybenzophenone by procedures described above and obtained as an extremely viscous oil: bp 125–126° (0.1 mm); ir (liquid) 3600 cm^{-1} (OH); nmr ($CDCl_3$) 5.35 (m, 2, =CH_2), 6.23 (s, 1, OH), 6.62–7.67 ppm (m, 9, ArH).

Synthesis of 1-(*o*-Hydroxyphenyl)-1,5-dienes. 1-(*o*-Hydroxyphenyl)-1,5-hexadiene (13a).—5-Bromo-1-pentene[22] was converted to the Grignard reagent, and a 0.1-mol portion in 50 ml of dry ether cooled in an ice bath and maintained under a nitrogen atmosphere was treated, dropwise, with 6.0 g of salicylaldehyde in 25 ml of dry ether over a period of 10 min. The thick, brown-yellow mixture was refluxed for 24 hr, cooled, treated with a saturated solution of ammonium chloride, and worked up to yield a crude product which was dissolved in benzene and chromatographed on a column containing 300 g of silica gel. Elution with a mixture of ether, benzene, and carbon tetrachloride (2:5:8) yielded a middle fraction consisting of 5.5 g (57% based on salicylaldehyde) of **17a** as a yellow oil: bp 100–102° (0.1 mm); nmr (CCl_4) δ 1.0–2.3 (m, 6, CH_2), 4.2 (s, 1, OH), 4.48–5.22 (m, 3, CHO and =CH_2), 5.35–6.12 (m, 1, =CH), 6.53–7.4 (m, 4, ArH), 8.3 (s, 1, ArOH). Samples of this oil, *ca.* 0.3 ml at a time, were injected through a serum cap into a 0.625 in. × 1 ft pyrolysis tube filled with type 110–5005 Superbrite glass beads (product of Minnesota Mining and Manufacturing Co.), maintained at 280–300°, and evacuated to *ca.* 0.1–0.3 mm of pressure. From 5.5 g of crude alcohol there was obtained, by this batchwise procedure allowing 5–10 min between injections, a total of 4.5 g (48–50% overall from salicylaldehyde) of crude product which, upon chromatography on alumina followed by distillation, yielded **13a** as a colorless oil, mp 78–79° (0.07 mm).

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.81, H, 8.06.

Purification *via* glc yielded (a) 9 parts of the trans isomer of **13a** [ir (liquid) 972 cm^{-1} (trans CH=CH); uv max (95% EtOH) 285 nm (ϵ 7700), 262.5 (shoulder, 12,000), 255 (14,000), and 214 (14,700)] and (b) 1 part of the cis isomer of **13a** [uv max (95% EtOH) 290 nm (ϵ 4100), 242.5 (11,700), and 215 (17,000)].

1-(*o*-Hydroxyphenyl)-1-phenyl-1,5-hexadiene (13b).—A solution of 0.2 mol of Grignard reagent from 5-bromo-1-pentene[22] in 100 ml of ether was treated, as described above, with 9.3 g of *o*-hydroxybenzophenone in 20 ml of ether. The reaction mixture was refluxed for 24 hr and worked up to give a crude product which, after chromatography on alumina [eluted with ether–heptane (1:9)] and distillation, yielded 6.6 g (52% based on benzophenone) of **13b** as a colorless oil: bp 126–127° (0.25 mm); uv max (95% EtOH) 210 nm (ϵ 15,600), 250 (8460), and 282.5 (shoulder, 2400); ir (liquid) 3600 (ArOH), 922 (=CH_2), 760 (1,2-disubstituted Ar), and 697 cm^{-1} (monosubstituted Ar); nmr (CCl_4) δ 1.72–2.42 (m, 4, CH_2), 4.69–5.17 (m, 3, =CH_2 and OH), 5.30–6.45 (m, 2, =CH and Ar_2C=CH), and 6.60–7.35 ppm (m, 9, ArH).

Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 85.71; H, 7.16.

1-(*o*-Hydroxyphenyl)-6-phenyl-1,5-hexadiene (13c).—Equimolar amounts of triphenylphosphine and 5-bromo-1-phenyl-1-

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(20) K. Fries and G. Fickewirth, *Ber.*, **41**, 367 (1908).

(21) H. E. Hennis, Ph.D. Dissertation, University of Missouri, 1956.

(22) H. B. Wood and E. C. Horning, *J. Amer. Chem. Soc.*, **75**, 5511 (1953).

pentene in benzene were stirred and heated at reflux for 72 hr, cooled, washed with benzene, and dried to give an 80% yield of triphenyl-1-pentenylphosphonium bromide, mp 203–205°. A suspension of 24.3 g of this compound in 200 ml of dry ether was treated, dropwise, with phenyllithium from 1.9 g of lithium and 15.7 g of bromobenzene in 15 ml of dry ether. To the vigorously stirred solution was slowly added 6.7 g of *o*-methoxybenzaldehyde in 25 ml of ether. After 16 hr of refluxing, the mixture was worked up to give a crude product which was purified by chromatography on 300 g of alumina [product eluted with ether–heptane (1:1)] followed by distillation to yield 6.6 g (60%) of 1-(*o*-methoxyphenyl)-6-phenyl-1,5-hexadiene (**22**) as a colorless oil, bp 153–155° (0.05 mm), which solidified and was recrystallized from heptane: mp 38–40°; ir (liquid) 965 (trans CH=CH), 752 (1,2-disubstituted Ar), and 962 cm^{-1} (monosubstituted Ar); uv max (95% EtOH) 213 nm (ϵ 24,300), 255 (29,200), 285 (5830), 293 (6390), and 300 (5530); nmr (CCl_4) δ 1.90–2.73 (m, 4, CH_2),3.53 (s, 3, OCH_3), and 5.35–7.50 ppm (m, 13, ArH and =CH).

Anal Calcd for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 85.92; H, 7.71.

Following a literature procedure,[23] a 4.0-g sample of **22** was added dropwise to a solution prepared from 14.1 g of methyl iodide and 2.8 g of magnesium in 80 ml of ether. The ether was removed by distillation, and the residue was heated for 2.5 hr at 155–160° and then treated with an ammonium chloride solution. Extraction with ether afforded a pale yellow oil which was chromatographed on 50 g of alumina. Elution with heptane–ether (3:1) followed by methanol–ether (1:6) yielded 3.0 g (75%) of **13c** containing only a trace of the benzopyran **19**. Recrystallization from heptane yielded 2.4 g of colorless crystals: mp 73–75°; ir (Nujol) 3680 (OH), 980 and 973 (trans CH=CH), 752 (monosubstituted and 1,2-disubstituted Ar), and 695 cm^{-1} (monosubstituted Ar); uv max (95% EtOH) 255 nm (ϵ 30,900), 285 (5400), 293 (6700), and 301 (6260); nmr (CCl_4) δ 1.85–2.70 (m, 4, CH_2), 5.22 (s, 1, OH), 5.60–7.50 ppm (m, 14, ArH and =CH).

Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.21; H, 7.39.

4-Phenyl-1,2,3,3a,4,9b-hexahydrocyclopenta[c][1]benzopyran (19).—A solution of 0.1 mol of Grignard reagent from 5-bromo-1-phenyl-1-pentene in 75 ml of ether was treated, as described above, with 5.5 g of salicylaldehyde. Chromatography of the crude product on silica gel using carbon tetrachloride–benzene–ether (8:5:2) as eluent yielded 1-phenyl-1-pentene in the first fraction, salicylaldehyde in the second fraction, and 7.0 g (60%) of the alcohol **17c** in the third fraction: nmr (CCl_4) δ 0.98–2.37 (m, 6, CH_2), 3.78 (s, 1, OH), 4.64 (t, 1, ArCHCH), 5.71–6.50 (m, 2, CH=CH), 6.55–7.35 (m, 9, ArH), and 8.21 ppm (s, 1, ArOH). Pyrolysis of a 5-g sample of this material under the conditions described above yielded 3.5 g of solid, mp 57–60° which was distilled [bp 141–143° (0.1 mm)] and recrystallized from methanol to give **19** as colorless, transparent plates: ir (Nujol) 756 (1,2-disubstituted Ar) and 700 cm^{-1} (monosubstituted Ar); uv max (95% EtOH) 220 nm (ϵ 9340), 260 (2710), 279.5 (3580), and 285 (3280); nmr (CCl_4) δ 1.00–2.93 (m, 8, CH and CH_2), 4.24 (d, J = 9.6 Hz) and 4.88 (d, J = 8.8 Hz) together account for 1 H (-OCHAr), and 6.56–7.51 ppm (m, 9, ArH).

Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.47; H, 7.28.

1-Benzyl-2-(*o*-hydroxyphenyl)cyclopentane (20).—Following a literature procedure[24] a solution of 0.25 g of **7** in 3 ml of dry pyridine was treated with 0.3 g of sodium metal, and the mixture was stirred and refluxed under a nitrogen atmosphere for 4 hr. Work-up gave 0.21 g of crude product which was distilled to yield 0.29 g (80%(of **8** as a viscous, pale yellow oil: bp 125° (0.1 mm); ir (liquid) 3600 cm^{-1} (ArOH); uv max (95% EtOH) 218 nm (ϵ 10,400), 270 (shoulder, 2300), 277 nm (2700), and 281 (shoulder, 2500); nmr (CCl_4) δ 1.08–3.58 (m, 10, CH_2), 4.58 (s, 1, OH), 6.35–7.44 (m, 9, ArH).

Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.35; H, 7.95.

***cis*-2-Butyl-3-phenyl-2,3-dihydrobenzofuran (28).**—Following published procedures, ω-phenoxyacetophenone[25] was converted to 3-phenylbenzofuran[26] and the latter was acylated.[27] A mixture of 4.0 g of 3-phenylbenzofuran, 4 ml of butyric anhydride, 3 ml of butyric acid, and 0.8 g of 85% phosphoric acid was stirred and heated at 100–105° for 44 hr. Chromatography of the crude product on alumina yielded 1 g of starting material and 2.6 g (64% based on recovered starting material) of 2-*n*-butyroyl-3-phenylbenzofuran (**26**) as a pale yellow oil, bp 146–148° (0.1 mm), which solidified on standing: mp 58–60° after recrystallization from heptane; ir (Nujol) 1685 cm^{-1} (C=O); uv max (95% EtOH) 208 nm (ϵ 14,300), 230 (15,200), and 300 (18,900); nmr (CCl_4) δ 0.92 (t, 3, CH_3), 1.30–2.05 (m, 2, CH_2), 2.83 (m, 2, CH_2), 6.90–7.79 ppm (m, 9, ArH).

Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.92; H, 6.24.

Huang-Minlon[28] reduction of a 5.5-g sample of **26** produced, after distillation, 4.5 g (86%) of 2-*n*-butyl-3-phenylbenzofuran (**27**) as a pale yellow oil which was chromatographed on alumina and distilled to give a colorless oil: bp 118–120° (0.1 mm); nmr (CCl_4) δ 0.63–2.05 (m, 7, CH_2 and CH_3), 2.76 [t, 2, -O(=C)-CH_2–], and 6.91–7.70 ppm (m, 9, ArH).

Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.14; H, 7.24.

A 1.8-g sample of **27** was mixed with 0.2 g of 10% palladium on charcoal catalyst and hydrogenated in 20 ml of absolute ethanol for 24 hr at 15 psi. Chromatography of the crude product on a column containing 200 g of alumina yielded starting material in the first fraction [eluted with heptane–ether (30:1)], a mixture of **25** and **27** in the middle fraction, and *cis*-2-butyl-3-phenyl-2,3-dihydrobenzofuran (**28**) in the last fraction (eluted with ether), obtained as 0.6 g of a colorless oil which solidified on standing: mp 63.5–64.5° after recrystallization from methanol; nmr (CCl_4) identical with that of the hydrogenation product from isomer B of **25** (see below).

Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.56; H, 8.03.

1-Phenyl-1-(*o*-hydroxyphenyl)hexane was prepared by reduction with hydrogen and 10% palladium on charcoal catalyst of 1-phenyl-1-(*o*-hydroxyphenyl)-1,5-hexadiene (**13b**) and was obtained as a colorless oil: bp 97–99° (0.1 mm); ir (liquid) 3600 cm^{-1} (ArOH); nmr (CCl_4) δ 0.59–1.00 (m, 3, CH_3), 1.00–2.36 (m, 8, CH_2), 4.21 (t, 1, J = 7.1 Hz, Ar_2CH), 4.75 (s, 1, OH), and 6.23–7.57 ppm (m, 9, ArH).

Anal. Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.49; H, 8.43.

Photolysis Experiments. Comparative Photolyses.—Samples of the 2-keto-2,3-dihydrobenzofurans or the *o*-hydroxystyrenes were dissolved in 400–500 ml of the specified solvent and were irradiated in a Rayonet Model RPR-100 reactor (product of Southern New England Ultraviolet Co., Middletown, Conn.) equipped with 2537-Å reactor lamps for 18 hr. The solvent was removed, and the crude product was analyzed by nmr to give the results recorded in Tables I and II.

The photolyses described below were carried out in an inert atmosphere in an apparatus of 300-ml capacity carrying a quartz immersion well containing a Hanovia 450-W medium-pressure lamp (product of Hanovia Co., Newark, N. J.).

Photolysis of 2-Keto-2,3-dihydrobenzofuran (3).—A 3.00-g sample of **3** in 280 ml of 2-propanol was irradiated for 5 hr, the 2-propanol was removed by distillation, the residue was distilled to yield 2.42 g of an oil, bp 46–49° (0.02 mm), and the oil was separated by glc (column 1) into unreacted starting material (55%) and isopropyl *o*-hydroxybenzyl ether (**4**, R = *i*-C_3H_7) (45%): uv max (95% EtOH) 275 nm (ϵ 2720); ir (liquid) 3400 cm^{-1} (OH); nmr (CCl_4) δ 1.17 [d, 6, J = 6.1 Hz, $CH(CH_3)_2$], 3.64 [septuplet, 1, J = 6.1 Hz, $CH(CH_3)_2$], 4.57 (s, 2, $ArCH_2$), and 7.56 ppm (s, 1, OH).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.18; H, 9.52.

Photolysis of 2-Keto-3,3-dimethyl-2,3-dihydrobenzofuran (5a). A. In Methanol.—A 4.20-g sample of **5a** in 279 ml of methanol was irradiated for 9 hr, during which time samples were withdrawn every hour to check the course of the reaction. The crude product consisted of 2.86 g of an oil, bp 54–57°, which was separated by glc (column 1; temperature 160°) into starting material (47%), product **a** (46%), and product **b** (7%). Product

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(24) J. Gripenberg and T. Hase, *Acta Chem. Scand.*, **20**, 1561 (1966).
(25) W. Davis and S. Middleton, *J. Chem. Soc.*, 822 (1958).
(26) J. N. Chatterjea and S. K. Roy, *J. Indian Chem. Soc.*, **40**, 144 (1963).
(27) N. P. Buu-Hoi, N. D. Xuong, and N. V. Bac, *J. Chem. Soc.*, 173 (1964).
(28) Huang-Minlon, *J. Amer. Chem. Soc.*, **68**, 2487 (1946).

a was identified as 2-(*o*-hydroxyphenyl)propene (**7a**) by comparison with an authentic sample (see above). Product **b** was identified as *o*-isopropylphenol (**8a**): ir (liquid) 3450 cm^{-1} (OH); nmr (CCl_4) δ 1.22 [d, 6, $CH(CH_3)_2$], 3.18 [septuplet, 1, $CH(CH_3)_2$], 5.38 (s, 1, OH), and 6.50–7.26 ppm (m, 4, ArH).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.71; H, 9.05.

2-Methoxy-2-(*o*-hydroxyphenyl)propane (**6a**, R′ = CH_3), although not isolated in pure form, was shown to be present in 38% amount in the crude product on the basis of the nmr (CCl_4): δ 1.57 [s, $C(CH_3)_2$], 3.18 (s, OCH_3), 6.42–7.35 (m, ArH), and 8.35 ppm (s, OH).

B. In 2-Propanol.—Irradiation of 1.71 g of **5a** in 281 ml of 2-propanol for 2.5 hr yielded 1.50 g of crude product which was shown by nmr analysis to contain unreacted starting material (53.5%), 2-(2-hydroxyphenyl)propene (**7a**) (40%), and 2-isopropoxy-2-(2-hydroxyphenyl)propane [**6a**, R″ = $CH(CH_3)_2$] (6.5%). That *o*-isopropylphenol must also be present is shown by the composition of a pyrolysate of the crude reaction product which contains starting material (55.5%), 2-(2-hydroxyphenyl)-propene (40.5%), and *o*-isopropylphenol (**8a**) (3.5%).

C. In *n*-Pentane.—Irradiation of 0.60 g of **5a** in 300 ml of *n*-pentane (Spectrograde) for 1 hr gave 0.50 g of a crude product which was separated by glc into unreacted starting material and 2-(2-hydroxyphenyl)propene (**7a**). Nmr analysis of the crude product indicated that it is comprised only of these two materials, present to the extent of 27.5 and 72.5%, respectively.

Photolysis of 2-Keto-3,3-diethyl-2,3-dihydrobenzofuran (5b). A. In Methanol.—Irradiation of 5.00 g of **5b** in 270 ml of methanol for 13 hr yielded, after distillation of the crude product, 4.18 g of a colorless oil, bp 55–57° (0.05 mm), which was separated by glc (column 1; temperature 182°) into starting material and a fraction which, upon further glc separation (column 2; temperature 133°), was resolved into two fractions. One of these was identified as a 91:9 mixture of (*E*)- and (*Z*)-3-(2-hydroxyphenyl)pentene-2 (**7b**): uv max (95% EtOH) 214 nm (ϵ 7220) and 279 (1860); ir (liquid) 3600 cm^{-1} (OH); nmr (CCl_4) δ 0.85 (t, J = 7.47 Hz) and 1.00 (t, J = 7.40 Hz) for 3 H of CH_2CH_3, 1.47 (doubled triplet, J = 1.30 and 6.61 Hz) for 2.74 H of $-CHCH_3$, 1.76 (d, J = 6.80 Hz) for 0.29 H of $=CHCH_3$, 2.28 (q, J = 7.40 Hz) for 2 H of CH_2CH_3, 5.01 (s, 0.85, OH), 5.81–5.86 (broad, 0.11, OH), 5.71 (quartet of triplets, J = 1.40 and 6.61 Hz, 0.85, $=CHCH_3$), 6.56–7.30 ppm (m, 4, ArH).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.16; H, 8.65.

The other fraction was identified as a 42:58 mixture of (*E*)- and (*Z*)-**7b**. Nmr analysis of the crude distillate showed that it was comprised of starting material (56.4%), (*E*)-3-(2-hydroxyphenyl)pentene-2 (35%), 3-methoxy-3-(2-hydroxyphenyl)pentane (**6b**, R″ = CH_3) (4.4%), and (*Z*)-3-(2-hydroxyphenyl)-pentene-2 (4.2%).

B. In 2-Propanol.—Irradiation of 1.45 g of **7b** in 280 ml of 2-propanol for 4 hr yielded a crude product containing 47% of 3-(2-hydroxyphenyl)pentene-2 (**7b**). Distillation of the crude product afforded 1.17 g of a pale yellow oil, bp 60–65° (0.02 mm), which glc analysis (column 2; temperature 110°) showed to be comprised of starting material (33%), (*E*)-3-(2-hydroxyphenyl)-pentene-2 (41.5%), and (*Z*)-3-(2-hydroxyphenyl)pentene-2 (15.5%).

C. In *n*-Pentane.—Irradiation of 6.07 g of **5b** in 2340 ml (six separate runs) for 1 hr yielded, after distillation, 5.50 g of a colorless oil, bp 70–77° (0.1 mm), which was shown by nmr analysis to contain unreacted starting material (57%), (*E*)-3-(2-hydroxyphenyl)pentene-2 (23%), and (*Z*)-3-(2-hydroxyphenyl)pentene-2 (20%).

Photolysis of 2-Keto-3-methyl-3-phenyl-2,3-dihydrobenzofuran (5c).—A 4.48-g sample of **5c** in 260 ml of methanol was irradiated for 6 hr, during which time aliquots were withdrawn to follow the course of the reaction. Distillation of the crude product yielded 2.45 g, bp 110° (0.07 mm), which was separated by glc (column 2; temperature 180°) into starting material and two other compounds. One of these was identified as 1-(*o*-hydroxyphenyl)-1-phenylethene (**7c**) by comparison. The other was identified as 1-(*o*-hydroxyphenyl)-1-phenylethane (**8c**): uv max (95% EtOH) 275.5 nm (ϵ 2680); ir (liquid) 3600 cm^{-1} (OH); nmr (CCl_4) δ 1.54 (d, 3, J = 7.33 Hz, CH_3), 4.28 (q, 1, J = 7.33 Hz, Ar_2CHCH_3), 4.70 (s, 1, OH), and 6.30–7.30 ppm (m, 9, ArH).

Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.63; H, 7.02.

Nmr analysis of the distilled product, before glc separation, indicated it to contain starting material (20%), 1-(*o*-hydroxyphenyl)-1-phenylethene (58.3%), and 1-(*o*-hydroxyphenyl)-1-phenylethane (9.7%). 1-Methoxy-1-(*o*-hydroxyphenyl)-1-phenylethane (**6c**, R″ = CH_3), although not isolated in pure form, was shown to be present as the major component of the undistilled reaction product: nmr (CCl_4) δ 1.76 (s, 3, Ar_2CCH_3), 3.16 (s, 3, OCH_3), 6.43–7.40 (m, 9, ArH), and 8.17 ppm (s, 1, OH).

Photolysis of 2-Keto-3-ethyl-3-phenyl-2,3-dihydrobenzofuran (5d).—A 1.79-g sample of **5d** in 280 ml of methanol was irradiated for 6 hr to give, after distillation, 1.35 g of a colorless oil, bp 112–114° (0.05 mm), which was separated by glc (column 2; temperature 167°) into starting material and a fraction containing four components. Passage of the latter fraction through column 1 (temperature 184.5°) yielded two fractions, the first of which contained a 1:1 mixture of the cis and trans isomers of 2-methyl-3-phenyl-2,3-dihydrobenzofuran (**9d**): uv max (95% EtOH) 281.5 nm (ϵ 3820); ir (liquid) absence of OH and C=O; nmr (CCl_4) δ 0.95 (d, 1.15, J = 6.4 Hz, CH_3), 1.43 (d, 1.5, J = 6.0 Hz, CH_3), 3.88–5.10 (m, 2, ArCH and OCH), and 6.50–7.50 ppm (m, 4, ArH).

Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.95; H, 6.91.

The second fraction contained a 5:2 mixture of the *E* and *Z* isomers of 1-phenyl-1-(*o*-hydroxyphenyl)propene-1 (**7d**), identified by comparison with an authentic sample (see above). Nmr analysis of the crude and distilled products showed their compositions to be identical, *viz.*, starting material (21.5%), 1-methoxy-1-phenyl-1-(2-hydroxyphenyl)propane (40%), (*Z*)-1-phenyl-1-(2-hydroxyphenyl)propene-1 (8.1%), (*E*)-1-phenyl-1-(2-hydroxyphenyl)propene-1 (7.8%), *cis*- (or *trans*-) 2-methyl-3-phenyl-2,3-dihydrobenzofuran (11.3%), and *trans*- (or *cis*-) 2-methyl-3-phenyl-2,3-dihydrobenzofuran (11.3%).

Photolysis Experiments. A. 1-(*o*-Hydroxyphenyl)-1,5-hexadiene (13a).—A solution of 0.90 g of **13a** in 180 ml of methanol was degassed by alternate evacuation and nitrogen flushing and then irradiated for 4.5 hr with a 550-W Hanovia arc contained in a quartz well. Aliquots removed at hourly intervals and analyzed by glc showed the following ratios of *cis*-**1a** to *trans*-**13a**: 1 hr, 61:39; 2 hr, 82:18, 3 hr, 78:22; 4 hr, 75:25. An nmr spectrum of the crude, undistilled product indicated it to consist of *ca.* two parts of olefin (*cis*- and *trans*-**13a**) and one part of the ether **23a**, the latter indicated by a singlet resonance at δ 3.25 (CH_3O) and a triplet resonance at 4.30 ppm (ArCH) with an intensity ratio of 3:1. Upon distillation, however, decomposition of **23a** to **13a** took place.

B. 1-(*o*-Hydroxyphenyl)-1-phenyl-1,5-hexadiene (13b).—A solution of 1.00 g of **13b** in 180 ml of methanol was degassed in the fashion described above and irradiated for 5.5 hr with a 550-W Hanovia arc contained in a quartz well. Removal of the solvent under vacuum at a temperature below 40° left a crude product which was shown by nmr spectral analysis to be lacking in starting material but to include some methoxyl-containing compound (presumably **23b**). Chromatography on alumina yielded 0.55 g of a colorless oil consisting of a mixture of *cis*- and *trans*-2-(4′-but-1-enyl)-3-phenyl-2,3-dihydrobenzofuran (**25**), bp 118° (0.05 mm).

Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.17; H, 7.14.

Rechromatography of **25** on alumina using heptane–ether (9:1) as the eluting solvent yielded isomer A of **25** in the first fraction and isomer B of **25** in the fourth fraction: nmr (CCl_4) of isomer A δ 1.60–2.73 (m, 4, CH_2), 4.16 [d, 1, J = 7.6 Hz, $(C_6H_5)_2CH$], 4.34–4.74 (m, 1, –OCH), 4.75–5.21 (m, 2, $=CH_2$), 5.43–6.13 (m, 1, CH=C), and 6.60–7.52 ppm (m, 9, ArH); nmr (CCl_4) of isomer B δ 1.00–1.59 (m, 2, CH_2), 1.78–2.45 (m, 2, CH_2), 4.42 [d, 1, J = 7.9 Hz, $(C_6H_5)_2CH$], 4.58–5.18 (m, 3, $=CH_2$ and –OCH), 5.32–6.07 (m, 1, CH=C), and 6.57–7.43 ppm (m, 9, ArH).

Hydrogenation of isomer A of **25** in the presence of 10% palladium on charcoal catalyst afforded 85% of the corresponding 2-*n*-butyl-3-phenyl-2,3-dihydrobenzofuran (**28**): nmr (CCl_4) δ 0.69–2.11 [m, 9, $-(CH_2)_3CH_3$], 4.13 [d, 1, J = 7.6 Hz, $(C_6H_5)_2CH$], 4.31–4.73 (m, 1, –OCH), and 6.53–7.57 ppm (m, 9, ArH).

Hydrogenation of isomer B of **25** under similar conditions afforded 85% of the corresponding 2-*n*-butyl-3-phenyl-2,3-dihydrobenzofuran (**28**), identical with the cis isomer of this compound (see above): nmr (CCl_4) δ 0.59–1.62 [m, 9, $-(CH_2)_3CH_3$], 4.40 [d, 1, J = 7.9 Hz, $(C_6H_5)_2CH$], 4.58–5.02 (m, 1, –OCH), 6.51–7.60 (m, 9, ArH). The detailed pattern of the

6.5–7.6-ppm region of isomer B is quite different from that of isomer A.

C. 1-(*o*-Hydroxyphenyl)-6-phenyl-1,5-hexadiene (13c).—A 0.55-g sample of pure, crystalline 13c in 180 ml of methanol was degassed in the fashion described above and irradiated for 1.5 hr with a 550-W Hanovia arc contained in a quartz well. The solvent was then removed, and the thick, orange, oily crude product was chromatographed on 50 g of alumina. Elution with ether–heptane (1:3) yielded only a trace of material, and elution with ether–methanol (6:1) yielded a yellow oil which was distilled, bp *ca.* 150° (0.1 mm), to give 0.21 g of a viscous, yellow oil: ir (liquid) 3400 cm^{-1} (ArCH); nmr (CCl_4) δ 1.2–2.7 (broad, 7, CH and CH_2), 3.12 (d, *ca.* 1, J = 1.2 Hz, ArCH), 3.23 (d, *ca.* 1, J = 2 Hz), and 6.5–7.3 ppm (m, 9, ArH). A sample of this material was treated with trifluorohexamethylsilylacetamide, and the silylated product was shown by glpc analysis to contain four components.

Registry No.—**3**, 553-86-6; **4** (R = *i*-Pr), 33316-78-8; **5a**, 13524-76-0; **5b**, 39477-78-6; **5c**, 4355-42-4; **5d**, 4374-69-0; **5e**, 39477-81-1; **6a**, 39477-82-2; **7a**, 10277-93-7; *cis*-**7b**, 39477-84-4; *trans*-**7b**, 39477-85-5; **7c**, 39477-86-6; *cis*-**7d**, 39477-87-7; *trans*-**7d**, 39477-88-8; **7e**, 39477-89-9; **8a**, 88-69-7; **8c**, 4237-44-9; *cis*-**9d**, 38281-39-9; *trans*-**9d**, 38281-40-2; **11b**, 17256-00-7; *cis*-**13a**, 39477-93-5; *trans*-**13a**, 39477-94-6; **13b**, 39477-95-7; **13c**, 39477-96-8; **17a**, 38865-45-1; **17c**, 39477-98-0; **19**, 39477-99-1; **20**, 39478-00-7; **22**, 39478-01-8; *cis*-**25**, 39478-02-9; *trans*-**25**, 39478-03-0; **26**, 39478-04-1; **27**, 39478-05-2; *cis*-**28**, 39478-06-3; *trans*-**28**, 39478-07-4; 2-keto-3-phenyl-2,3-dihydrobenzofuran, 3117-37-1; *o*-hydroxyacetophenone, 118-93-4; *o*-hydroxybenzophenone, 117-99-7; *p*-hydroxybenzophenone, 1137-42-4; 5-bromo-1-pentene, 1119-51-3; salicylaldehyde, 90-02-8; triphenylphosphine, 603-35-0; 5-bromo-1-phenyl-1-pentene, 37464-87-2; triphenyl-1-pentenylphosphonium bromide, 39478-10-9; *o*-methoxybenzaldehyde, 135-02-4; 1-phenyl-1-(*o*-hydroxyphenyl)hexane, 39478-11-0.

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Quenching and Reduction of Photoexcited Benzophenone by Thioethers and Mercaptans[1]

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Reactions of thioethers (sulfides) with excited triplet benzophenones have been studied (1) by retardation by the sulfides of photoreduction by isoborneol, (2) by quenching by naphthalene of photoreduction by the sulfides, and (3) by quenching of phosphorescence of the ketone by the sulfides. Quenching rate constants, k_{ir}, are in the range 10^7–10^9 M^{-1} sec^{-1}. They are highest for aliphatic and lowest for aromatic sulfides, and values are decreased by α branching and by electronegative substituents, and higher in acetonitrile than in benzene. Benzophenone is photoreduced by sulfides containing α H. Quantum yields are low, $\varphi \sim 0.05$–0.2, and increase with decreasing values of k_{ir}. Quenching of phosphorescence of benzophenone by mercaptans shows values of k_q in the range 10^7–10^9 M^{-1} sec^{-1}, highest for aromatic, lowest for aliphatic thiols, decreased by electron-attracting substituents. Reversible hydrogen abstraction is not important in reactions of sulfides, while probably dominant in reactions of thiols. Quenching and photoreduction by sulfides may proceed *via* a common charge transfer complex, in which a full unit of charge separation is not developed. Contributions of charge transfer, hydrogen transfer, and polarizability in quenching and reduction of excited carbonyl compounds by alcohols, ethers, amines, sulfides, and mercaptans are discussed.

The photoreduction of benzophenone to benzopinacol by alcohols proceeds by abstraction of hydrogen by the excited ketone triplet[2] from the α carbon of the alcohol, eq 1, and reduction of ground-state benzophenone by

$$(C_6H_5)_2C{=}O(T_1) + RR'CHOH \rightleftharpoons (C_6H_5)_2\dot{C}OH + RR'\dot{C}OH \quad (1)$$

the alcohol derived radical, eq 2. Such photoreductions are inhibited by mercaptans or disulfides, present in low concentration, by hydrogen transfer reactions which, in effect, catalyze disproportionation of the initially formed radicals, eq 3 and 4. Ketone and alcohol are regenerated, while the sulfur compounds are regenerated in their alternate oxidation states and function repeatedly, each molecule of sulfur compound negating the effects of many quanta. Support for this mechanism was found in racemization of optically active alcohols[3] and in introduction of carbon-bound deuterium into alcohols[4] during the mercaptan-inhibited reaction, but not during uninhibited photoreduction. Mercaptans might also retard the photoreduction more directly if the excited ketone abstracted sulfhydryl hydrogen from S of mercaptan and the resulting radicals disproportionated, eq 4. At appropriate high concentrations of alcohol and low concentration of thiols the sequence of reactions, eq 1, 3, 4, can be shown to occur almost exclusively.[5]

$$(C_6H_5)_2C{=}O + RR'\dot{C}OH \longrightarrow (C_6H_5)_2\dot{C}OH + RR'C{=}O \quad (2)$$

$$RR'\dot{C}OH + ASH \longrightarrow RR'CHOH + AS\cdot \quad (3)$$

$$(C_6H_5)_2\dot{C}OH + AS\cdot \longrightarrow (C_6H_5)_2C{=}O + ASH \quad (4)$$

The borneols are effective photoreducing agents for benzophenone, leading to camphor and benzopinacol

(1) A preliminary report of part of these results has been published: J. B. Guttenplan and S. G. Cohen, *Chem. Commun.*, 247 (1969).

(2) G. S. Hammond and W. M. Moore, *J. Amer. Chem. Soc.*, **81**, 6334 (1959).

(3) S. G. Cohen, S. Orman, and D. A. Laufer, *ibid.*, **84**, 3905 (1962).

(4) S. G. Cohen, D. A. Laufer, and W. V. Sherman, *ibid.*, **86**, 3060 (1964).

(5) A. Rose, Ph.D. Thesis, Brandeis University, 1971.

in equimolar yields.[6] In analogy to the racemizations, it was of interest to us to examine the equilibration of the epimeric borneol and isoborneol in mercaptan-inhibited photoreductions, a study which will be described at a later date. The process proved complex, a rather high concentration of mercaptan was required, and it became apparent that direct interaction of excited ketone with mercaptan, probably including physical quenching, was occurring in this system in addition to inhibition by the hydrogen transfer reactions. This indicated that thioethers might act as quenchers without the added complexity of transfer of sulfhydryl hydrogen. We had not considered this earlier since we had observed that diphenyl sulfide had essentially no effect on the photoreduction of benzophenone by 2-propanol.[3] We now wish to report on quenching by mercaptans and on quenching and photoreduction by thioethers, reactions analogous in some respects to those of excited ketone with tertiary amines.[7]

Experimental Section

Materials.—Acetonitrile (Matheson Coleman and Bell spectroquality), benzene (Eastman Spectrograde), benzophenone (Fisher reagent grade, mp 47–48°), and naphthalene (Baker) were used directly. Phenyl methyl sulfide (Matheson Coleman and Bell), phenylthiol (Eastman), ethyl benzyl, phenyl benzyl, di-*sec*-butyl, and di-*tert*-butyl sulfides (Aldrich), thiophene, and diphenyl sulfide (Eastman) all showed less than 1% impurity by glc and were used directly. Anisole (Eastman) was collected by glc on a 20-ft Carbowax 20M column. Di-*n*-butyl sulfide (Eastman) was collected by glc on a 6-ft 10% adipate column. *p*-Chlorothiophenol (Aldrich) was crystallized from 95% ethanol and from petroleum ether (bp 60–80°), mp 48–49°. Isoborneol (Matheson Coleman and Bell) was crystallized from ethanol–water, mp 218–220° (sealed tube). Argon was dried over Drierite.

Irradiation Procedure.—Solutions were prepared in volumetric flasks. Aliquots, 2–5 ml, were transferred to calibrated Pyrex tubes, either 12-mm-o.d. round or 10-mm-i.d. square tubes, fitted with Fisher–Porter Teflon greaseless valves. Some tubes had 1-mm quartz absorption cells sealed to side arms. Tubes were degassed by three freeze–thaw cycles, Dry Ice–acetone, 20–100 μ, and closed under argon. Studies of rates of photoreduction were carried out on a turntable holding 12 tubes 8 cm from a G.E. H85/A3 lamp. Residual benzophenone, after periods of irradiation, was determined from the absorbance at 343 nm (ϵ 133) in benzene, measured in a 1-mm cell on a Beckman DU spectrometer. In study of photoreductions retarded by naphthalene or sulfides slopes of dependence of inverse quantum yield on concentration of retarder were obtained by least-squares analysis. Intercepts, inverse quantum yields in the absence of quencher, were taken from the study of the dependence of quantum yield on the concentration of reducing agent in the absence of quencher.

Monochromatic irradiations, for determination of quantum yields by ferrioxalate actinometry,[8] were carried out on a Bausch and Lomb 38-86-01 grating monochromator, dispersion 3.2 nm/mm, Osram SP-200 mercury vapor point source, with a square tube inserted into a cell holder at the exit slit. Solutions were stirred magnetically and cooled by an air blower. At wavelengths below 366 nm a Corning 7-54 filter was placed at the exit slit to filter scattered visible light which might be absorbed by the actinometer solution. Actinometer solutions were stirred and stoppered but not degassed. Ferrioxalate solutions and sample solutions were irradiated alternately several times to minimize effects of lamp fluctuation. Solutions for which quantum yields were determined in this way were used as secondary actinometers for irradiation on the turntable.

Phosphorescence spectra were obtained with 375-nm excitation on a Farrand Mark II spectrofluorimeter. Solutions were degassed in cylindrical quartz cells, ~1 cm o.d., fitted with Teflon stopcocks. Benzophenone concentrations were 0.05–0.10 M, and I_0/I ratios were in the range 1–10. A correction, ~3%, was applied for apparent emission resulting from scattered excitation light. Tubes were calibrated and marked so that they could be positioned reproducibly in the cell holder. Variations in phosphorescence intensity from duplicate samples was less than 2%.

Results

In preliminary experiments quantities of sulfides leading to ~0.01 M solutions were diluted with a solution of 0.06 M benzophenone and 0.10 M isoborneol in benzene. Aliquots were irradiated on a turntable along with a solution containing no sulfide and rates of photoreduction were determined (Table I).

TABLE I
PHOTOREDUCTION OF 0.06 M BENZOPHENONE BY 0.1 M ISOBORNEOL. EFFECTS OF ORGANIC SULFIDES

Registry no.	Sulfide Compd	Sulfide M	R_S/R_0[a]
544-40-1	Di-*n*-butyl	0.009	0.33
6263-62-3	Ethyl Benzyl	0.007	0.44
100-68-5	Phenyl Methyl	0.008	0.62
110-02-1	Thiophene	0.010	0.66
626-26-6	Di-*sec*-butyl	0.007	0.78
831-91-4	Phenyl Benzyl	0.010	0.81
107-47-1	Di-*tert*-butyl	0.008	0.85
139-66-2	Diphenyl	0.008	0.94

[a] Ratio of rates of photoreduction in presence and absence of sulfide.

The sulfides decreased the rate of photoreduction. They do not absorb a significant fraction of the light in the concentrations used and the effect is not due to masking. The di-*n*-aliphatic sulfide was the most effective retarder. Comparison of the *n*-butyl, *sec*-2-butyl, and *tert*-butyl sulfides indicates that the effect is decreased by α branching, which might be due to less or no α H or to a steric effect.

The retarding effect appears not to be due to reversible hydrogen abstraction. Two benzene solutions, 0.0024 M in benzophenone, the first containing 0.14 M isoborneol and the second containing 0.0074 M di-*n*-butyl sulfide, were subject to flash excitation. Both solutions contained sufficient additive, isoborneol or sulfide, to quench ~90% of the benzophenone triplets. The solution containing the isoborneol showed an intense long-lived (~1 msec) absorption at 545 nm, consistent[9] with a high yield of ketyl radical. The solution containing the sulfide showed essentially no such absorption, indicating at least an order of magnitude less of ketyl radical.

Comparison of retardations (Table I) due to *n*-butyl and ethyl benzyl sulfides, and phenyl methyl and phenyl benzyl sulfides, indicates that the electronegative phenyl attached to α C decreases the retardation. Comparison of the effects of ethyl benzyl, phenyl benzyl, and diphenyl sulfides indicates that the aromatic group linked to S strongly decreases the retarding effect. The low retardation due to diphenyl sulfide is consistent with its having led to no detected retardation in photoreduction of benzophenone by neat 2-propanol (13 M).[3] Thiophene which, strictly

(6) S. G. Cohen and R. J. Baumgarten, *J. Amer. Chem. Soc.*, **89**, 3471 (1967).

(7) S. G. Cohen and N. M. Stein, *ibid.*, **93**, 6542 (1971).

(8) C. G. Hatchard and C. A. Parker, *Proc. Roy. Soc., Ser. A*, **235**, 518 (1956).

(9) J. A. Bell and H. Linschitz, *J. Amer. Chem. Soc.*, **90**, 165 (1968).

speaking, does not lie in the class of sulfides shows moderate retarding activity.

Quantitative information about the retardation by sulfides may be obtained by detailed study of the photoreduction by the alcohol and by comparison of the effects on it of sulfides with that caused by a physical quencher of known efficiency, naphthalene. Photoreduction of 0.071 M benzophenone by varying concentrations of isoborneol in benzene was studied, and the concentrations and quantum yields were as follows: 0.050 M, φ 0.85; 0.080, 1.03; 0.10, 1.14; 0.25, 1.35; 0.50, 1.67; 1.0, 1.78. From these data a linear plot of $1/\varphi$ *vs.* $1/[RH]$ may be constructed,[10] consistent with eq 5. Least-squares analysis leads to the intercept

$$1/\varphi = 1/a + k_d/ak_{ir}[RH] \quad (5)$$

0.56 and the limiting quantum yield a, 1.8, and to the slope 0.032 M. The ratio of slope to intercept is obtained, $k_d/k_{ir} = 0.057$ M, the ratio of rate constant for self- and solvent-induced decay of triplet to that for abstraction of hydrogen by the triplet from the carbinol carbon of isoborneol, RH.

Rates of photoreduction of benzophenone by isoborneol in benzene and in acetonitrile, as affected by naphthalene and by two sulfides, di-*n*-butyl sulfide and phenyl methyl sulfide, were determined. The results are summarized in Tables II and III. The

TABLE II

RETARDATION BY NAPHTHALENE OF PHOTOREDUCTION OF 0.060 M BENZOPHENONE BY 0.20 M ISOBORNEOL

Solvent	[Naphthalene] × 10³, M	Quantum yield
C_6H_6[a]	1.6	0.23
C_6H_6	4.0	0.13
C_6H_6	11.0	0.052
C_6H_6	16.0	0.034
C_6H_6	21.0	0.029
CH_3CN	1.0	0.21
CH_3CN	4.1	0.057
CH_3CN	7.6	0.033
CH_6CN	19.1	0.013

[a] Rates of photoreduction of benzophenone by 0.2 M isoborneol in the absence of quencher are the same in C_6H_6 and in CH_3CN.

data may be described by a Stern–Volmer relation, eq 6, in which k_q is the rate constant for quenching of the

$$1/\varphi = 1/a + k_d/ak_{ir}[RH] + k_q[Q]/ak_{ir}[RH] \quad (6)$$

triplet by the additive Q. The slope of the plot of $1/\varphi$ *vs.* $[Q]$ is $k_q/ak_{ir}[RH]$ and the ratio of slope to intercept is $k_q/(k_d + k_{ir}[RH])$. The ratio, k_d/k_{ir}, is known from the preceding experiments and the values of k_q/k_{ir} may be calculated. The data in Table II for quenching by naphthalene lead to values of slope of 1.64×10^3 M^{-1} in benzene and 4.0×10^3 M^{-1} in acetonitrile, and to ratios of k_q/k_{ir} of 590 in benzene and 1290 in acetonitrile. The value of k_d/k_q in benzene is 0.97×10^{-4} M, similar to that observed with benzhydrol[10a] as reducing agent, 1.03×10^{-4} M.

Quenching of benzophenone triplet by naphthalene, essentially diffusion controlled,[11] has a value of k_q in

TABLE III

RETARDATION BY SULFIDES OF PHOTOREDUCTION OF 0.060 M BENZOPHENONE BY 0.17 M ISOBORNEOL

Solvent	Sulfide	[Sulfide] × 10³, M	Quantum yield
C_6H_6	DBS[a]	1.9	0.98
C_6H_6	DBS	4.7	0.58
C_6H_6	DBS	8.4	0.40
C_6H_6	DBS	19.0	0.22
CH_3CN	DBS	0.82	0.64
CH_3CN	DBS	3.2	0.45
CH_3CN	DBS	5.5	0.28
CH_3CN	DBS	19.0	0.12
CH_3CN	DBS	24	0.10
C_6H_6	PMS[b]	2.7	1.24
C_6H_6	PMS	7.0	1.02
C_6H_6	PMS	15.0	0.81
C_6H_6	PMS	26.0	0.68
CH_3CN	PMS	3.4	0.75
CH_3CN	PMS	7.0	0.50
CH_3CN	PMS	16.0	0.33
CH_3CN	PMS	23.0	0.27

[a] DBS = di-*n*-butyl sulfide. [b] PMS = phenyl methyl sulfide.

benzene[12] of 6.3×10^9 M^{-1} sec^{-1}. This leads to $k_{ir} = 1.07 \times 10^7$ M^{-1} sec^{-1} for abstraction of hydrogen by benzophenone triplet from isoborneol in benzene, $k_d = 6 \times 10^5$ sec^{-1}. A value of $k_q = 1.1 \times 10^{10}$ M^{-1} sec^{-1} for k_q in acetonitrile, based on its lower viscosity, leads to $k_{ir} = 0.9 \times 10^7$ M^{-1} sec^{-1} in this solvent, similar to the value in benzene. The data in Table III lead to values of slope, of k_q/k_{ir}, and of k_q for quenching by the sulfides, based on the values of k_{ir} determined above. Results are summarized in Table IV.

TABLE IV

RETARDATION BY NAPHTHALENE AND BY SULFIDES OF PHOTOREDUCTION OF 0.06 M BENZOPHENONE BY ~0.2 M ISOBORNEOL IN BENZENE AND IN ACETONITRILE

Quencher	Solvent	Slope, M^{-1}	k_q/k_{ir}	$k_q \times 10^{-8}$, M^{-1} sec^{-1}
Naphthalene	C_6H_6	1.64×10^3	590	63
Naphthalene	CH_3CN	4.0×10^2	1440	110
DBS[a]	C_6H_6	200	61	6.6
DBS[a]	CH_3CN	370	113	9.6
PMS[b]	C_6H_6	29	8.9	0.9
PMS[b]	CH_3CN	127	39	3.3

[a] Di-*n*-butyl sulfide. [b] Phenyl methyl sulfide.

The sulfides are effective retarders, and they are more efficient in acetonitrile than in benzene. Their rates are substantially less than diffusion controlled, and therefore their greater efficiency in acetonitrile may not be ascribed to the lower viscosity of this solvent. It may indicate a polar contribution to the mechanism of quenching by the thioethers.

If the thioethers act as quenchers of the ketone triplets and not by some other mechanism, such as that of eq 3 and 4, they compete with the alcohol reducing agent for the triplets, and their quenching effectiveness should depend on (a) the concentration and (b) the reactivity toward the triplet of the reducing agent. Application of eq 6 to a system containing varying concentration of isoborneol and constant concentration of

(10) (a) W. M. Moore, G. S. Hammond, and R. P. Foss, *J. Amer. Chem. Soc.*, **83**, 2789 (1961); (b) W. M. Moore and M. D. Ketchum, *ibid.*, **84**, 1368 (1962).

(11) K. Sandros and H. L. J. Bäckstrom, *Acta Chem. Scand.*, **16**, 958 (1962).

(12) W. D. Clark, A. D. Litt, and C. Steel, *J. Amer. Chem. Soc.*, **91**, 5413 (1969).

a thioether as quencher would lead to a linear plot of $1/\varphi$ *vs.* 1/[RH] with slope equal to $(k_d + k_q[Q])/ak_{ir}$. Table V contains data for two such experiments.

TABLE V

EFFECT OF CONCENTRATION OF ISOBORNEOL ON PHOTOREDUCTION IN BENZENE OF 0.071 *M* BENZOPHENONE[a]

Isoborneol	Phenyl methyl sulfide, quantum yield, φ	Ethyl benzyl sulfide, quantum yield, φ
0.050	0.50	
0.052		0.38
0.068		0.44
0.080	0.70	
0.10	0.73	0.53
0.14		0.64
0.20		0.83
0.25	1.16	
0.39		0.95
1.0	1.54	

[a] In the presence of (1) 0.0073 *M* phenyl methyl sulfide and (2) 0.0053 *M* ethyl benzyl sulfide.

The data at 0.1 *M* and higher concentration of isoborneol do lead to linear plots. For phenyl methyl sulfide the slope is 0.086 *M* and $k_q = 1.5 \times 10^8\ M^{-1}$ sec^{-1} similar to that found above by variation in concentration of sulfide. For ethyl benzyl sulfide the slope is 0.13 *M* and $k_q = 3.7 \times 10^8\ M^{-1}\ sec^{-1}$. This value is intermediate between the values for phenyl methyl sulfide and di-*n*-butyl sulfide in benzene (Table IV), consistent with the relative effectiveness of these three compounds as retarders (Table I). At lower concentrations of isoborneol the plots of $1/\varphi$ *vs.* 1/[RH] deviate from linearity in the direction of high quantum yields. As will be shown below, the sulfides are also weak photoreducing agents; this contributes more importantly to the total photoreduction at low concentrations of isoborneol, and this may account for the deviation.

The dependence of the effectiveness of quenching by the sulfide on the reactivity of the alcohol reducing agent is seen in comparative experiments with isoborneol and 2-propanol. In photoreduction of 0.060 *M* benzophenone by 0.50 *M* alcohol reducing agent in benzene, the ratio of rates in the presence and absence of 0.0045 *M* di-*n*-butyl sulfide was 0.60 when isoborneol was the alcohol, 0.40 when 2-propanol was the alcohol. The greater retarding efficiency of the sulfide in reduction by 2-propanol is consistent with the lower reactivity of this alcohol toward benzophenone triplet, $k_{ir} = 1.8 \times 10^6\ M^{-1}\ sec^{-1}$,[13] as compared with $1.07 \times 10^7\ M^{-1}\ sec^{-1}$ for isoborneol.

Analysis of photoreduction solutions inhibited by sulfides indicated that these compounds were not merely quenchers, since they were slowly consumed during the reactions. In a photoreduction of 0.060 *M* benzophenone by 0.18 *M* isoborneol in acetonitrile in the presence of 0.0070 *M* phenyl methyl sulfide, disappearance of benzophenone was followed at 343 nm, and formation of camphor from isoborneol and decrease in concentration of sulfide were followed by glc. After 40-min irradiation 0.024 *M* benzophenone was reduced, 0.011 *M* camphor was formed, and 0.0020 *M* sulfide disappeared. The sulfide had reduced the quantum yield from 1.25 to 0.50, preventing photoreduction of ~0.048 *M* benzophenone by isoborneol or quenching ~0.024 *M* triplet. Of this it appeared to lead to photoreduction of ~0.002 *M* triplet, indicating an efficiency or approximate quantum yield for photoreduction by phenyl methyl sulfide of ~0.08. Similarly, in a photoreduction of 0.060 *M* benzophenone by 0.17 *M* isoborneol in benzene in the presence of 0.0084 *M* di-*n*-butyl sulfide the quantum yield was reduced from 1.25 to 0.40. After 90-min irradiation 0.046 *M* benzophenone was reduced and 0.0032 *M* sulfide was consumed. This sulfide apparently prevented photoreduction of ~0.123 *M* benzophenone by isoborneol, quenching ~0.062 *M* triplet and photoreducing ~0.0032 *M* triplet. This indicates an efficiency or approximate quantum yield for photoreduction by di-*n*-butyl sulfide of ~0.05.

This interpretation was examined by study of the photoreduction of benzophenone by these sulfides. Rates of photoreduction of 0.060 *M* benzophenone by 0.077 *M* phenyl methyl sulfide in acetonitrile and by 0.19 *M* di-*n*-butyl sulfide in benzene were measured on the turntable simultaneously with a photoreduction by isoborneol of known quantum yield. The results indicated quantum yields of 0.06 and 0.05 for photoreduction by the two sulfide systems, respectively, in adequate agreement with those calculated above from consumption of the sulfides as they retarded photoreduction by isoborneol. Quantum yields were also obtained similarly for photoreduction of benzophenone by 0.049 *M* ethyl benzyl sulfide in benzene, $\varphi = 0.06$, by 0.10 *M* phenyl methyl sulfide in benzene, $\varphi = 0.13$, and by 0.088 *M* *p*-chlorophenyl methyl sulfide in benzene, $\varphi = 0.20$. These quantum yields for photoreduction by di-*n*-butyl sulfide and phenyl methyl sulfide, and probably ethyl benzyl sulfide, would differ little from high concentration limiting values, because of the high values of k_{ir} which characterize their reactions measured as k_q values (Table IV). *p*-Chlorophenyl methyl sulfide with an electron-attracting substituent has a lower value of k_{ir}, $1.7 \times 10^7\ M^{-1}\ sec^{-1}$, measured below, by phosphorescence quenching, and the limiting quantum yield for photoreduction by this compound would be 0.22. It may be noted that all the values of k_{ir} are rather high; the quantum yields are relatively low and appear to fall with increasing values of k_{ir}. The stoichiometry of photoreduction by sulfides in benzene was examined briefly. Irradiation of 0.05 *M* benzophenone and 0.050 *M* benzyl ethyl sulfide for 5 hr led to reduction of 0.013 *M* benzophenone and consumption of 0.15 *M* sulfide; irradiation of 0.05 *M* benzophenone and 0.44 *M* phenyl methyl sulfide led to consumption of 0.020 *M* benzophenone and 0.021 *M* sulfide. Approximately equimolar consumption of ketone and sulfide was indicated.

The photoreduction of 0.06 *M* benzophenone by 0.019 *M* di-*n*-butyl sulfide was then examined in the presence of a quencher for this reaction, naphthalene, leading by a second procedure to the value of k_{ir} for interaction of the sulfide with benzophenone triplet. The following results were obtained, the first number in each pair being the concentration of naphthalene, the second the quantum yield for photoreduction: 0.0, 0.049; 0.00031, 0.046; 0.00086, 0.033; 0.0024, 0.025; 0.0060, 0.014. The plot of $1/\varphi$ *vs.* concentra-

(13) S. G. Cohen and A. D. Litt, *Tetrahedron Lett.*, 837 (1970).

tion of naphthalene was linear, slope = $8.5 \times 10^3\ M^{-1}$, intercept = 20.5, ratio of slope to intercept 415 M^{-1}, and the rate constant for interaction of benzophenone triplet with di-*n*-butyl sulfide, $k_{ir} = 7.6 \times 10^8\ M^{-1}\ sec^{-1}$, based on k_q for naphthalene, $6.3 \times 10^9\ M^{-1}\ sec^{-1}$. The value of k_{ir} for interaction of benzophenone triplet with di-*n*-butyl sulfide used as a photoreducing agent thus proves quite similar to that found through its use as a quencher for photoreduction (Table IV), $6.6 \times 10^8\ M^{-1}\ sec^{-1}$.

During the course of this work it was observed that phosphorescence of benzophenone in solution at room temperature could be used to determine values of k_{ir} or k_q for quenching of benzophenone triplet, and applications of this have been published.[12,13] This procedure has now been applied to some sulfides, allowing comparison with the values determined in the photoreduction experiments, and to some mercaptans. The latter may not be studied by the photoreduction methods. Values of k_q have been obtained from phosphorescence intensities in the absence and presence of added sulfur compound, I_0 and I, respectively, the triplet lifetime τ, 5×10^{-6} sec in benzene at 23°,[12] and application of the Stern–Volmer expression (eq 7) and are given in Table VI.

$$I_0/I = 1 + \tau_0 k_q[Q] \qquad (7)$$

TABLE VI

QUENCHING OF PHOSPHORESCENCE OF BENZOPHENONE TRIPLET BY SULFIDES AND MERCAPTANS IN BENZENE AT 23°

Registry no.	Sulfur compd	k_q, M^{-1} sec^{-1}
123-09-1	*p*-Chlorophenyl methyl sulfide	2.2×10^7
	Phenyl methyl sulfide	6.0×10^7
	Di-*tert*-butyl sulfide	5.0×10^7 (1.4×10^8)[a]
	Di-*n*-butyl sulfide	8.3×10^8 (1.7×10^9)[a]
107-03-9	*n*-Propylthiol	1.3×10^7
106-54-7	*p*-Chlorophenylthiol	2.0×10^8
108-98-7	Phenylthiol	2.6×10^8
1541-10-2	2,4,6-Trimethylphenylthiol	6.8×10^8
	Isoborneol	0.9×10^7

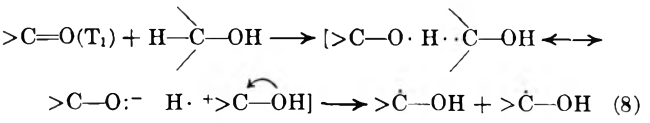
[a] Values in parentheses were measured in acetonitrile.

The value of k_q for phenyl methyl sulfide measured by phosphorescence quenching is similar to that found through its use as a quencher for photoreduction by isoborneol (Table IV). The quenching rate is decreased by the electron-attracting *p*-Cl substituent. The value for di-*n*-butyl sulfide is similar to those found through its use as a quencher (Table IV) and when studied as a photoreducing agent, quenched by naphthalene. Where measurements were made in both benzene and acetonitrile, quenching rates were higher in acetonitrile. The mercaptans prove to be efficient quenchers for benzophenone triplet. The aromatic thiols were more reactive than the aliphatic, and reactivity was decreased by the electron-attracting *p*-Cl substituent and increased by methyl substituents. The value of k_q for isoborneol is similar to that found by quenching by naphthalene of its reaction with benzophenone triplet.

Discussion

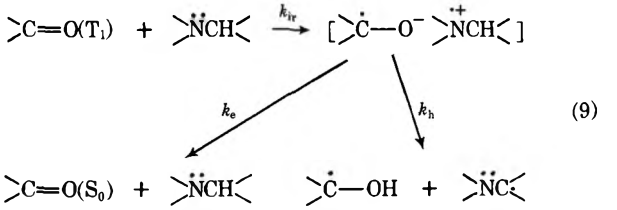
Thioethers may be very efficient quenchers and inefficient reducing agents for excited benzophenone. The rate constants for the interaction, k_{ir}, are in the range 10^7–$10^9\ M^{-1}\ sec^{-1}$, generally higher than those for alcohols and lower than those for amines. The values are greater in acetonitrile than in benzene and indicate a polar contribution to the mechanism, which may involve interaction of triplet ketone with nonbonding electrons of sulfur. These are made less available by electron-attracting and aromatic groups, the presence of which decrease values of k_{ir}. Quantum yields for photoreduction are low, 0.05–0.20, much lower than those for alcohols and amines which may commonly be larger by an order of magnitude.

We have proposed that photoreduction by alcohols proceeds by abstraction of hydrogen from carbon α to the hydroxyl, facilitated by a polar contribution from the heteroatom,[14,15] eq 8, while photoreduction by



(8)

amines proceeds *via* rapid charge transfer type interaction of triplet ketone with the n electrons of nitrogen, k_{ir}, followed either by spin inversion, charge destruction and quenching, k_e, or by hydrogen transfer and electron reorganization, k_h, eq 9.[14,16] This has been



(9)

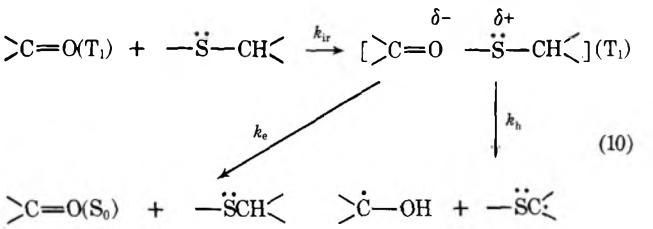
accepted as a rather common mechanism,[17] but reduction and quenching by two independent reactions leads to a similar formal kinetic scheme to that from reaction *via* a charge transfer complex, eq 9, and the two kinds of processes cannot be distinguished kinetically.[18]

In the process of eq 8 quantum yield is determined essentially by the relative values of k_r and k_d, rate constants for abstraction of hydrogen and for decay of triplet. In the process of eq 9, k_{ir} may be very high compared with k_d, and quantum yield is determined by the relative values of k_e and k_h. However polar effects are present in both processes and a single linear relationship may be observed, in reactions with a single acceptor, *i.e.*, triplet benzophenone, between value of log k_{ir} for a large variety of organic compounds—including both alcohols and amines—and the ionization potentials of these electron donors, IP_D.[19] Polar contributions to the kinds of processes represented by eq 8 and 9 may be similar at the transition states, or the log relationship may be too crude to distinguish between them.

It is reasonable to consider that reactions of thioethers follow a course related to that of eq 9, an initial polar interaction, which will now be indicated as for-

(14) S. G. Cohen and J. I. Cohen, *J. Phys. Chem.*, **72**, 3782 (1968).
(15) S. G. Cohen and J. I. Cohen *J. Amer. Chem. Soc.*, **89**, 164 (1967).
(16) S. G. Cohen and H. M. Chao, *ibid.*, **90**, 165 (1968).
(17) S. G. Cohen, A. Parola, and G. H. Parsons, Jr., *Chem. Rev.*, **73**, 141 (1973).
(18) S. G. Cohen, G. A. Davis, and W. D. K. Clark, *J. Amer. Chem. Soc.*, **94**, 869 (1972).
(19) J. B. Guttenplan and S. G. Cohen, *ibid.*, **94**, 4040 (1972).

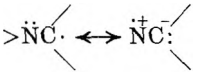
mation of partial charges, leading then either to quenching or to reduction, eq 10. This formulation,



(10)

as with amines, is consistent with high values of k_{ir} and low sensitivity to diffusion-controlled physical quenchers and allows for very low quantum yields. Triplet–triplet energy transfer, leading to quenching and to inefficient photoreduction, appears not to be a feasible mechanism. Sulfides absorb at much higher energy than benzophenone and their triplet energies are likely to be quite high. Also, the low quantum yields may apparently not be attributed to rapid disproportionation of products formed in an efficient initial hydrogen abstraction. Such a sequence might regenerate starting materials and lead to a low observed quantum yield, but the flash photolysis experiment with di-*n*-butyl sulfide indicates that this is not occurring. Study of photoreduction by an optically active amine indicated that this reversible hydrogen abstraction was not important in that photoreduction,[15] but deuterium-labeling experiments indicated that it did occur in photoreduction by an ether.[20]

The value of k_{ir} for reaction of di-*n*-butyl sulfide with excited benzophenone lies on the same linear plot of log k_{ir} *vs.* IP_D as do many amines,[19] supporting a process such as that of eq 10. However factors which affect the characteristics of these reactions of sulfides may differ from those affecting amines. The low quantum yields, corresponding to low k_h/k_e ratios, may result from low k_h and may indicate that S does not facilitate transfer of H and stabilization of radicals as effectively as N. Radical character α to N may be stabilized by resonance, which lowers the transition state energy for the hydrogen transfer. Such a contribution would be



less from S due to diminished overlap between orbitals of different principal quantum number. It may also be that k_e is higher for thioethers than for amines.

The nature of the initial complex indicated in eq 10 is not clear. The enthalpy for formation of a full charge transfer complex in a hydrocarbon solvent, ΔH_c, may be calculated[21] from

$$\Delta H_c = -\Delta E_{0,0} + [E(D/D^+) - E(A^-/A)] + 0.13 \text{ eV} \quad (11)$$

where $E(D/D^+)$ is the oxidation potential of the donor sulfide, $-E(A^-/A)$ is the reduction potential of the ground state acceptor ketone, and $\Delta E_{0,0}$ is the excitation energy. Oxidation potentials of thioethers do not appear to be reported, but they may be related to ionization potentials,[21] IP_D, by

$$IP_D = E(D/D^+) - \Delta G_{solv}(D^+) + C \quad (12)$$

in which $-\Delta G_{solv}(D^+)$ is the free energy for process 13,

$$D^+_g + D_s \rightleftharpoons D^+_s + D_g \quad (13)$$

and C reflects the reference electrode. Comparison of oxidation potentials[22] and ionization potentials[23] of compounds of similar size indicates a value of ~6.5 eV for $[-\Delta G_{solv}(D^+) + C]$ against saturated calomel electrode. The ionization potential of di-*n*-butyl sulfide is 8.3 eV, and $E(D/D^+) \simeq 1.8$ eV. With values of -1.73[24] and 2.97 eV[25] for the reduction potential and triplet energy, respectively, of benzophenone, AH_c is ~15 kcal/mol above triplet benzophenone. The entropy of complex formation is also unfavorable, -18 eu,[26] and the resulting free energy of activation would lead to rate constants much lower than those observed in this work. Thus a complex involving transfer of a full unit of charge is not involved in this process. The effect on k_{ir} of change in solvent from hydrocarbon to acetonitrile is also much less in these reactions than when a full charge is formed.[27]

A similar calculation for the interaction of benzophenone triplet with amines led to a similar conclusion;[19] the observed rates were far too high to be due to transfer of a full unit of charge, and the solvent effects were also too small. It was proposed that the interaction involved development of a partial charge and partial transfer of hydrogen, and this chemical reactivity contributed to the high value of k_{ir}. Quinuclidine, in which the bridgehead nitrogen may not facilitate hydrogen transfer well, is an inefficient photoreducing agent and has a value of k_{ir} an order of magnitude lower than would be predicted from its ionization potential.[19] On the other hand, electron donors which have very easily transferred hydrogen, phenols, anilines, and aromatic thiols, show quenching rates which are higher than would be predicted from the linear relation between log k_{ir} and IP_D. These indications that interaction with n electrons and partial transfer of hydrogen both contribute to the value of k_{ir} support the proposal that the quenching and hydrogen abstraction processes proceed *via* a common intermediate.

The aliphatic sulfides show values of k_{ir} consistent with their ionization potential,[19] but their chemical reactivity is low and partial transfer of hydrogen may not contribute substantially to the high quenching activity. The greater polarizability or heavy atom effect of sulfur, with increased spin–orbit coupling, may enhance intersystem crossing from excited triplet to ground state singlet, in effect increasing k_e, eq 10. The effect need not be a very large one, since with aliphatic amines quenching and hydrogen transfer, k_e and k_t, are already delicately balanced and may be processes of similar rate.

Quenching interactions may involve charge transfer,

(20) S. G. Cohen and S. Aktipis, *J. Amer. Chem. Soc.*, **88**, 3587 (1966).

(21) D. Rehm and A. Weller, *Z. Phys. Chem., Neue Folge*, **69**, 183 (1970), and references cited therein.

(22) L. A. Hull, G. T. Davis, D. H. Rosenblatt, and C. K. Mann, *J. Phys. Chem.*, **73**, 2142 (1969).

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(24) M. Peover in "Electroanalytical Chemistry," Vol. 2, A. J. Bard, Ed., Marcel Dekker, New York, N. Y., 1967, p 9.

(25) J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," Wiley, New York, N. Y., 1966, p 298.

(26) H. Knibbe, D. Rehm, and A. Weller, *Ber. Bunsenges. Phys. Chem.*, **73**, 839 (1969).

(27) H. Leonhardt and A. Weller, *ibid.*, **67**, 791 (1963).

partial hydrogen transfer, and polarization. Since there may be a polar effect on hydrogen transfer,[14] all three factors may be related to ionization potential, and many compounds show a linear relation between log k_{ir} and IP_D.[19] The absolute value of k_{ir} depends as well on the acceptor and this has been formulated, eq 14, in a relation derived from eq 11. While for a single

$$\log k_{ir} \simeq -{}^3\Delta E_{0,0} + IP_D - E(A^-/A) + C' \qquad (14)$$

acceptor and a series of donors log $k_{ir} \simeq IP_D$, for a single donor and series of acceptors log $k_{ir} \simeq -{}^3\Delta E_{0,0} - E(A^-/A)$.[28] The relative importance of the several possible factors in a particular interaction will be affected by the properties of the donor–acceptor pair. The extent to which hydrogen donation will contribute will depend on the triplet energy of the acceptor and the C–H bond strength in the donor. Interactions with phenols, anilines, or aromatic thiols will show much hydrogen transfer, and this effect will be greater if the acceptor has high triplet energy. The extent to which electron transfer will contribute will depend on the reduction potential and anionic stability of the acceptor and the oxidation or ionization potential of the donor. Interactions of an acceptor of favorable reduction potential such as fluorenone will show much electron transfer, and this effect will be greater if the donor does not have readily transferred hydrogen, such as di-*tert*-butyl sulfide or quinuclidine. The extent to which polarizability will contribute will depend on atomic size in the donor–acceptor pair and the oxidation and reduction potentials. Where electron-attracting substituents in the donor lower the charge transfer and polarization contributions to the transition state, hydrogen transfer contributions may become proportionally more important. This may account for the inverse relationship between k_{ir} and quantum yield for photoreduction observed in reactions of the thioethers.

Values of rate constants for interaction of mercaptans with excited ketones have not been accessible through study of them as reducing agents or quenchers. These compounds have readily extractable sulfhydryl hydrogen, but they are not photoreducing agents for ketones. When the abstraction occurs, it is followed efficiently by exothermic disproportionation and regeneration of ground state ketone and mercaptan, eq 4. Although mercaptans retard photoreduction by alcohols[3,4] and amines,[15] such study does not lead to values of k_q since the retardation may be due largely or wholly to hydrogen transfer reaction eq 3 and 4. They do interact with excited ketone, and values of k_q, now determined by quenching of phosphorescence (Table VI), indicate high reactivity, $k_q \simeq 10^7$–10^9 M^{-1} sec^{-1}. The greater reactivity of the aromatic as compared with aliphatic thiols, opposite to what is observed in the sulfides, indicates that hydrogen transfer from thiol to triplet contributes importantly to the quenching interaction. This would be favored by greater stability of aromatic thiyl radical. This effect may account for the values of k_q for aromatic thiols being greater than would be indicated by their ionization potentials. Decrease and increase in reactivity by electron-withdrawing and -donating substituents, respectively, while small, indicate some polar contribution to the interaction. This may be an effect on interaction of triplet with n electrons of S or an effect on the polar contribution to the hydrogen transfer.

The values of k_q for mercaptans now allow approximate calculation of the relative importance of retardation of photoreduction by mercaptans by the two processes, quenching of excited ketone, and catalysis of disproportionation, eq 3 and 4. For the aromatic thiol with highest value of k_q, 6.8×10^8 M^{-1} sec^{-1} (Table VI), in photoreduction by neat, 13 M 2-propanol, for which $k_r = 1.8 \times 10^6$ M^{-1} sec^{-1}, at 0.005 M thiol about 13% of the retardation may be due to direct interaction of mercaptan and ketone triplet, the remainder due to the hydrogen transfer reactions, eq 3 and 4.

A comparison may be made of interaction and subsequent reaction of excited carbonyl compounds with compounds of O, N, and S. Because of the high electronegativity of O, interaction apparently does not take place at the n electrons, but starts with abstraction of H from α C, and is facilitated by a polar contribution in the transition state, eq 8. Alcohols are not quenchers, but ethers may exhibit disproportionation of the radicals formed by hydrogen transfer. High O–H and lower α-C–H bond energies strongly favor abstraction of α C–H. With amines lower electronegativity and ionization potentials leads to interaction at the n electrons, and interaction between the n electrons and an unpaired electron on adjacent C facilitates transfer of α C–H to excited carbonyl, but the amines may also quench, eq 9. With mercaptans, polarizability and low ionization potential lead to interaction at S, and low S–H bond energy and low capacity of S to stabilize an adjacent radical lead to transfer of sulfhydryl hydrogen to excited ketone. With sulfides, the polarizability of S and low stabilization of the α-carbon radical lead to interaction at S and then largely to quenching, and to little transfer of hydrogen.

Registry No.—Benzophenone, 119-61-0; isoborneol, 124-76-5; naphthalene, 91-20-3.

Acknowledgment.—We are pleased to acknowledge support of this research by the National Science Foundation, assistance from Professor H. Linschitz and Dr. M. Toth in carrying out flash photolysis experiments, and helpful discussions with Professor C. Steel.

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The Deuterium Isotope Effect and Migratory Aptitudes in the Clemmensen Reduction of 1-Indanones

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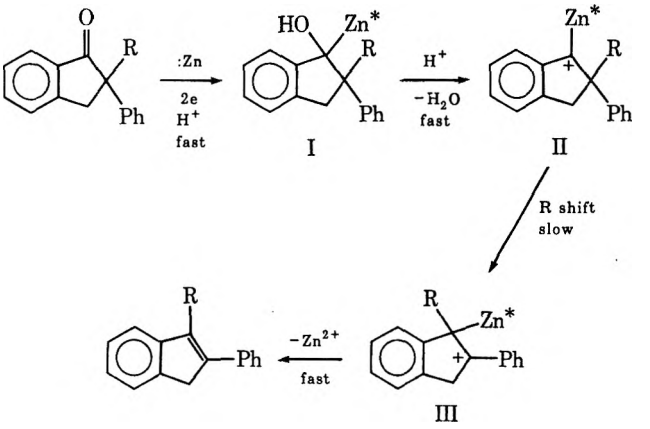
2-Phenyl-1-indanone-*2-d* (**4**) was reduced to 2-phenylindan-*1,1,2-d*$_3$ (**5**) and 2-phenylindene-*3-d*$_1$ (**6**), while 2-phenyl-1-indanone (**1**) under identical conditions gave 2-phenylindan (**2**) and 2-phenylindene (**3**), both in the ratio of 3:1. Kinetic measurements were carried out by following the increase in optical density for the formation of olefins. K_H/K_D was found to be 1.53. Reduction of 2-methyl-2-phenyl-1-indanone (**10**) gave 2-methyl-2-phenylindan (**11**) and 2-methyl-3-phenylindene (**12**), showing that the phenyl group migrated preferentially. 2,3,3-Triphenyl-1-indanone (**7**) under identical conditions gave 1,1,2-triphenylindan (**8**) and 1,1,2-triphenylindene (**9**). The formation of **3** and **6** shows that hydrogen migrates better than phenyl. The low isotope effect and the migratory aptitude of H > phenyl > methyl support the proposed mechanism.

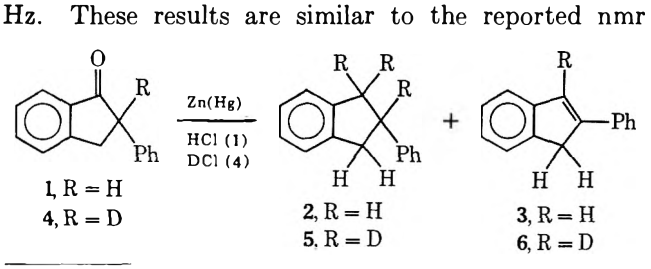
In a previous paper on the reductive rearrangements of 1-indanones and 1,3-indandiones under Clemmensen conditions it was reported that rearranged indenes form sometimes as major products of the reduction along with unrearranged indans.[2] Davis and coworkers have proposed the formation of cyclopropanediol intermediates in the Clemmensen reduction of α,β-unsaturated ketones[3,4] and 1,3 diketones.[3-6] The formation of such intermediates, however, is excluded in the indan system on steric grounds. Indeed, no such intermediates, or rearranged ketonic products arising from them, have been observed. A mechanism for saturated and unsaturated hydrocarbon formation was proposed, where rearranged olefin formation occurs with hydride or phenyl migration from the 2 to the 1 position of an intermediate cation on the surface of zinc.[2] It was the purpose of this study to establish a 1,2-hydride shift in rearranged olefin formation and to study the migratory aptitudes of hydrogen, phenyl, and methyl in this system in order to gain further support for the proposed mechanism.[2] For simplicity 1-indanones were chosen for the deuterium studies, as the deuterated indene **6** uniquely arises from such a mechanism (Scheme I). Zn* denotes the zinc surface.

SCHEME I



Results and Discussion

Clemmensen Reduction of 2-Phenyl-1-indanone (1) and 2-Phenyl-1-indanone-*2-d*$_1$ (4).—Deuteration of 2-phenyl-1-indanone (**1**) was carried out by exchange in DCl–D_2O and toluene to give **4**. That the exchange was complete was confirmed by its nmr, which showed only two types of protons, methylene and phenyl protons, in the ratio of 2:9. In addition, the spectrum showed a geminal coupling constant for the C-3 protons $J_{AB} = -17.5$ Hz, $\delta_{H_B} = 214.86$ Hz, and $\delta_{H_A} = 191.14$ Hz. These results are similar to the reported nmr spectrum[7] of 2-methyl-1-indanone-*2-d*$_1$, which showed for the methylene protons in this AB type system a coupling constant $J_{AB} = -17.6$ Hz, $\delta_{H_B} = 152$ Hz, and $\delta_{H_A} = 192$ Hz.



1, R = H
4, R = D

2, R = H
5, R = D

3, R = H
6, R = D

Clemmensen reduction of **1** and **4** under identical conditions gave saturated hydrocarbons **2** and **5**, and also olefins **3** and **6** in the ratio of 3:1, as determined by vapor phase chromatography.

The structures of **2** and **3** have already been established,[8,9] while the structures of **5** and **6** were determined by their nmr spectra. 2-Phenylindan-*1,1,2-d*$_3$ (**5**) showed a geminal coupling constant $J_{AB} = -16$ Hz, $\delta_{H_B} = 195.53$ Hz, and $\delta_{H_A} = 180.47$ Hz for the C-3 protons, while 2-phenylindene-*3-d*$_1$ (**6**) showed a 2 H singlet at δ 3.78 for the C-1 protons. Both compounds **5** and **6** showed phenyl protons at δ 7.00–7.72.

To detect any possible exchange of hydrogens in the product 2-phenylindene-*3-d*$_1$ (**6**), particularly that of the benzylic C-1 hydrogens, compound **3** (the undeuterated olefin) was subjected to Clemmensen reduction conditions in DCl–D_2O. Compound **3** was recovered unchanged as determined by its nmr.

Since according to the proposed mechanism[2] olefin formation involves a 1,2-hydride shift, the deuterium isotope effect for this reaction was determined. Rate of olefin formation was followed by ultraviolet spectroscopy. The ratio of the first-order rate constant (*i.e.*, the isotope effect) calculated (see Experimental Section) was 1.53. The deuterium isotope effect for

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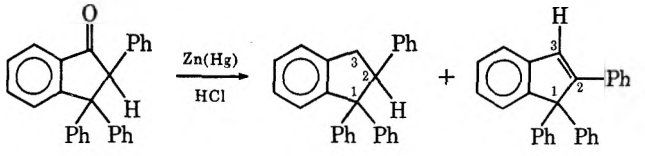
the abstraction of a proton (ionic reaction) is found to be higher, about four to ten.[10,11] It was reported by Hawthorne and Lewis[12a] that the isotope effect K_H/K_D in the hydrolysis of pyridine diphenylborane was 1.53, while Wiberg[10] in his study of the Cannizzaro reaction reported an isotope effect of 1.8. These authors have stated that as a rule small isotope effects are observed for hydride transfer reactions. In the proposed scheme for olefin formation, the rate-determining step involves a C–H bond breakage only in going from II to III. The isotope effect can be attributed only to this step. Thus the low isotope effect found in this study indicates that a hydride transfer is involved in rearranged olefin formation and is in accord with the proposed mechanism.

Reduction of 2,3,3-Triphenyl-1-indanone (7).—The reduction of this compound was undertaken to further demonstrate that the 3 position of 1-indanones is not involved in the reduction to saturated hydrocarbon as well as to rearranged olefins. Clemmensen reduction of **7** gave two components.

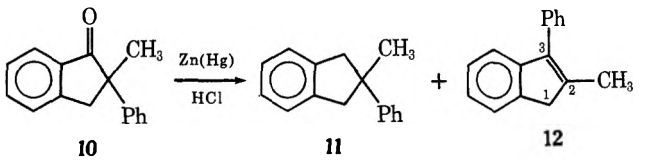


7 **8** **9**

The first component was 1,1,2-triphenylindan (**8**) whose nmr spectrum showed a 2 H doublet at δ 3.12 for the C-1 proton (J = 8.5 Hz), a 1 H triplet at δ 4.70 for the C-2 protons (J = 8.5 Hz), and a 19 H multiplet for the phenyl protons centered at δ 6.97 (6.11–7.83). Elemental analysis was in accord with this structure.

The second component of this reduction was an indene, to which, based on spectral data, the structure of 1,1,2-triphenylindene (**9**) was assigned. This compound has not been reported in the literature. The nmr spectrum of compound **9** showed a complex multiplet at δ 7.03 (6.50–7.53) for the phenyl protons, which includes the vinylic C-3 proton.

Reduction of 2-Methyl-2-phenyl-1-indanone (10).—From the reduction of 2-methyl-2-phenyl-1-indanone (**10**) the compounds 2-methyl-2-phenylindan (**11**) and

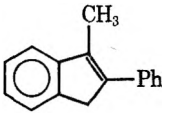


10 **11** **12**

2-methyl-3-phenylindene (**12**) were obtained in the ratio of 3:1, as determined by vapor phase chromatography, along with some unchanged starting material. Separation of the first component **11** was achieved by column chromatography, followed by distillation of the petroleum ether (bp 30–60°) fraction. The nmr spectrum (in CCl_4) showed a geminal coupling constant J_{AB} = −15 Hz, δ_{H_B} = 198.82 Hz, and δ_{H_A} = 180.58 Hz (C-1 protons); J_{AB} = −15 Hz, δ_{H_B} = 198.82 Hz, and δ_{H_A} = 180.58 Hz (C-3 protons), indicating that the protons on C-1 and C-3 are equivalent; a 3 H singlet for C-2 methyl protons at δ 1.31 and a 9 H multiplet at δ 7.10 (6.83–7.41) for the phenyl protons. Elemental analysis further confirmed this compound to be **11**.

The second component, believed to be 2-methyl-3-phenylindene (**12**), could not be isolated from the reduction mixture as a pure compound. It distilled off together with the indan **11** from which it could not be separated. It has already been reported that 2-phenyl-3-methylindene (**13**) is a solid (lit.[13] mp 75–77°) and that 2-methyl-3-phenylindene (**12**) is an oil [lit.[14] bp 149–150° (0.5 mm).

The ultraviolet spectrum indicated the presence of olefin **12**, showing a λ_{max} at 267 nm. This was different from the uv spectrum observed for 2-phenyl-3-methylindene (**13**), which showed λ_{max} at 293 nm (reported[14] for **13** λ_{max} 293 nm and for **12** λ_{max} 263 nm).



13

In addition it was shown by vapor phase chromatography that the olefin **12** obtained in this reduction mixture was not identical with 2-phenyl-3-methylindene (**13**), which was prepared independently,[15] as shown by their different retention times. Thus, it is believed that the olefin obtained in this reduction mixture was 2-methyl-3-phenylindene (**12**), as predicted by the proposed mechanism.[2] Migration of both groups from the C-2 carbon have not been observed in previous reductions and seem unlikely.

Relative migratory aptitudes to a carbonium ion in the pinacol system have been described to be in the order of hydrogen > aryl > alkyl group.[16] That a phenyl group migrated preferentially to an alkyl group was also shown in the acid-catalyzed dehydration of indanols.[14] Thus, where C-2 is disubstituted, there is a competition between an aromatic substituent and an alkyl substituent to migrate to C-3. Generally, the migration of the aromatic radical is observed.[14] This is the case noted in the dienone–phenol[17] rearrangement, in the dehydration of pinacols,[18] and in solvolysis.[19]

That hydrogen migrates preferentially to phenyl was shown by the formation of 2-phenylindene (**3**)[2] as the only olefin formed from the reduction of 2-phenyl-1-indanone (**1**). It was further found in this study that phenyl migrated rather than methyl in the formation of 2-methyl-3-phenylindene (**12**) from 2-methyl-2-phenyl-1-indanone (**10**). Thus, it was shown that under Clemmensen conditions phenyl migrated better than methyl and hydrogen migrated better than phenyl, indicating that hydrogen migration occurs with a pair of electrons (hydride shift). The possibility exists of these rearrangements occurring in a nonlinear activated complex where the C–H bending rather than the

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(11) (a) R. P. Bell, "Acid-Base Catalysis," Oxford University Press, New York, N. Y., 1941, p 146; (b) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1967, p 72.

(12) (a) M. F. Hawthorne and E. S. Lewis, *J. Amer. Chem. Soc.*, **80**, 4296 (1958). (b) S. Winstein and J. Takahashi, *Tetrahedron*, **2**, 316 (1958); V. J. Shiner, *et al.*, *J. Amer. Chem. Soc.*, **87**, 1382 (1965).

(13) O. Blum-Bergman, *Ber.*, **65B**, 109 (1932).

(14) H. Christol, C. Martin, and M. Mousseron, *Bull. Soc. Chim. Fr.*, 1696 (1960).

(15) H. A. Bruson and H. L. Plant, *J. Org. Chem.*, **32**, 3356 (1967).

(16) J. March, "Advanced Organic Chemistry," McGraw-Hill, New York, N. Y., 1968, p 788.

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(18) M. Tiffeneau and A. Orekhoff, *Bull. Soc. Chim. Fr.*, **35**, 1639 (1924).

(19) D. J. Cram and J. Allinger, *J. Amer. Chem. Soc.*, **79**, 2858 (1957).

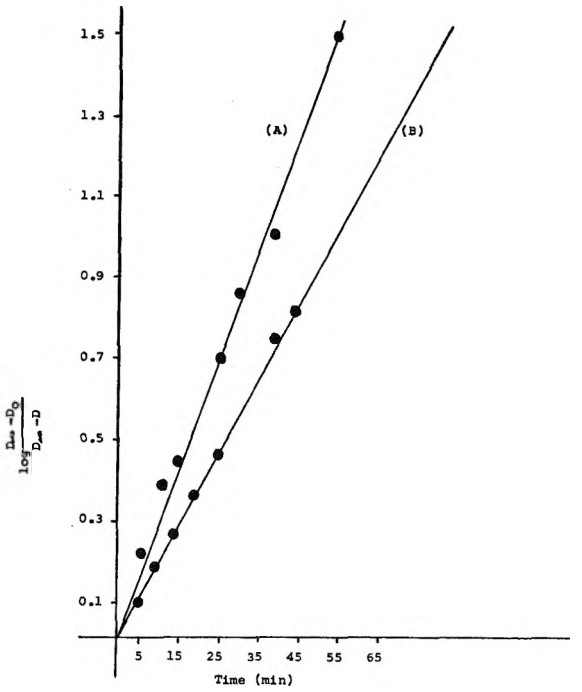

Figure 1.—Rate of olefin formation in the Clemmensen reduction of 2-phenyl-1-indanone (curve A) and 2-phenyl-1-indanone-2-d_1 (curve B).

stretching frequencies are dominant.[12] Such complexes would give rise to low K_H/K_D values. The above migratory aptitudes, however, support a hydride transfer mechanism.

Alcohols as intermediates have not been rigorously excluded from the proposed mechanism for reduction of above ketones. However, the preliminary vpc studies following the course of reaction from beginning to end do not show the appearance of any such intermediates. Further, more detailed studies on the nature of other possible intermediates are now being conducted.

Experimental Section

Infrared spectra were determined on a Perkin-Elmer 421 spectrophotometer. Ultraviolet spectra were run on a Perkin-Elmer 202 spectrophotometer. Nmr spectra were run on a A-60 spectrometer. Vapor phase chromatographic analyses were obtained on a F & M gas chromatograph. Melting points were determined on a Thomas-Hoover melting point apparatus. For kinetic measurements a Beckman D. U. spectrophotometer was used. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Starting Materials.—2-Phenyl-1,3-indandione and 2,3-diphenyl-1-indenone (for the preparation of 7) were purchased from Aldrich Chemical Co., Milwaukee, Wis. 1,2,2-Trichloropropane was obtained from K & K Laboratories, Plainview, N. Y. Deuterium chloride (38% in D_2O) and deuterium oxide (99.8% D) were purchased from Mallinckrodt Chemical Works, St. Louis, Mo.

2-Phenyl-1-indanone (1)[20] was prepared by the $AlCl_3$-catalyzed cyclization of 2,3-diphenylpropanoyl chloride,[21] mp 74–76° (lit.[22] mp 76–78°), and was purified by recrystallization from methanol.

2-Phenylindene (3) and 2-phenylindan (2) were prepared by the Clemmensen reduction of 2-phenyl-1,3-indandione.[2]

2,3,3-Triphenyl-1-indanone (7) was prepared by the procedure of Koelsch,[23] nmr ($CDCl_3$) δ 5.13 (1 H, singlet, C-2 protons) and 7.17 (6.30–8.05) (19 H, multiplet, phenyl protons).

2-Methyl-2-phenyl-1-indanone (10) was prepared according to Bruson and Plant,[15] nmr (CCl_4) J_{AB} = −17.5 Hz, δ_{HB} = 212.78 Hz, and δ_{HA} = 193.22 Hz (C-3 protons), δ 7.34 (6.86–7.83) (9 H, multiplet, phenyl protons), 1.54 (3 H, singlet, methyl protons).

2-Phenyl-3-methylindene (13) was prepared in accord with the procedure of Blum-Bergman,[13] nmr (CCl_4) δ 1.80 (3 H, triplet, methyl protons, J = 2 Hz), 3.16 (2 H, quartet, C-1 protons, J = 2 Hz), 6.92 (6.54–7.30) (9 H, multiplet, phenyl protons). Similar methyl triplets at 2.2–2.5 ppm and methylene quartets at 3.6–3.8 ppm (J = 2 Hz) have been reported for other methyl indenes.[20,24]

Preparation of 2-Phenyl-1-indanone-2-d_1 (4).—To a solution of 15 g (72 mmol) of 2-phenyl-1-indanone (1) in 60 ml of toluene was added 21 ml of D_2O (99.8% D) and 45 ml of DCl (38% in D_2O) with constant stirring at room temperature. The reaction mixture was refluxed overnight (24 hr). The organic phase was washed twice with D_2O and evaporated, thus leaving a cream-colored solid (14.8 g, 70 mmole, 97.2%) of 4, mp 74–76°.

Clemmensen Reductions. 2-Phenyl-1-indanone-2-d_1 (4).—A solution of 1 g of mercuric chloride in 15 ml of D_2O (99.8% D) was acidified with 0.5 ml of DCl (38% in D_2O). To this solution was added 10 g of granular zinc. After 15 min of stirring, the liquid was decanted and the residual amalgamated zinc was washed with D_2O. To this zinc amalgam was added a solution of 5 g (23 mmol) of 2-phenyl-1-indanone-2-d_1 (4) in 40 ml of toluene, 7 ml of D_2O, and 45 ml of DCl. The reaction mixture was refluxed overnight. The pale yellow toluene phase was then separated. Vapor-phase chromatography of this toluene phase of the reduction mixture on a polyethylene ether column (programming from 100 to 230° at 8°/min temperature rise) showed two peaks in the ratio of 3:1.

After the toluene was removed under reduced pressure, separation of the two components was achieved by column chromatography using Florisil (550 g, 100–200 mesh). In the petroleum ether fraction, after evaporation of the solvent, shiny white flakes were observed suspended in an oily medium. On addition of 5 ml of cold petroleum ether, shiny white flakes crystallized out and the colorless oil, after evaporation of the solvent, was distilled *in vacuo* (2 mm, 147–157°) [3.75 g (19 mmol), 75%, calculation based on vpc ratio]. Vpc retention time proved this compound to correspond to the first peak, which was identified as 2-phenylindan-1,1,2-d_3 (5), nmr (CCl_4) J_{AB} = 16 Hz, δ_{HB} = 195.53 Hz, and δ_{HA} = 180.47 Hz (C-3 protons), δ 7.13 (7.00–7.26) (9 H multiplet, phenyl protons).

Anal. Calcd for $C_{15}H_{11}D_3$: C, 91.31; H, 5.62. Found: C, 91.25; H, 5.98.

The second component (shiny white flakes) was recrystallized from 20 ml of benzene, mp 165–166°. This compound had identical retention time with that of the second peak of the reaction mixture, and was identified as 2-phenylindene-3-d_1 (6) [1.25 g (6 mmol), 25%, calculations based on vpc ratio], nmr (CCl_4) δ 3.78 (2 H, singlet, C-1 protons), 7.35 (9 H, multiplet, phenyl protons).

Anal. Calcd for $C_{15}H_{11}D$: C, 93.21; H, 5.74. Found: C, 90.99, 92.77, 92.45; H, 5.93, 5.75, 6.71.

2-Phenylindene (3) in D_2O and DCl.—This reaction was run under the same conditions as described above. After 24-hr reaction the organic layer was separated. Analyses of the yellow toluene phase by vpc gave one peak with the same retention time as that of the starting material, mp 166–168° (lit.[9] mp 167.5°). The infrared and nmr spectra were identical with that of the unchanged starting 2-phenylindene (3).

2,3,3-Triphenyl-1-indanone (7).—The same reduction procedure was followed as described above, using H_2O–HCl instead of D_2O–DCl.

Thin layer chromatography of the toluene phase (MN silica gel S-HR, UV_{254} plates) showed two components in the reaction mixture which were separated by column chromatography using Florisil (550 g, 100–200 mesh). The petroleum ether fraction gave 1.3 g (3 mmol, 26%) of a white solid, identified as 1,1,2-triphenylindan (8), mp 134–135°.

Anal. Calcd for $C_{27}H_{22}$: C, 93.59; H, 6.40. Found: C, 93.47; H, 6.60.

The second component, 2,3,3-triphenylindene (9), was present in the petroleum ether–benzene (1:1) eluate. The light green solid was crystallized from 30 ml of benzene to give 0.2 g (0.5 mmol, 4%) of 2,3,3-triphenylindene (9).

2-Methyl-2-phenyl-1-indanone 10.—The same procedure for

(20) L. L. Miller and R. F. Boyer, *J. Amer. Chem. Soc.*, **93**, 646 (1971).
(21) N. Campbell and E. Ciganek, *J. Chem. Soc.*, 3834 (1956).
(22) S. Goldschmidt and B. Acksteiner, *Chem. Ber.*, **91**, 502 (1958).
(23) C. F. Koelsch, *J. Org. Chem.*, **3**, 456 (1938).
(24) N. D. Heindel, S. N. Lemke, and W. A. Mosher, *J. Org. Chem.*, **31**, 2680 (1966).

reduction was followed as described above. The toluene phase of the reduction mixture was found to be composed of three components in the ratio of 3:1:2.7 as detected by vpc on a polyethylene glycol column (programmed from 100 to 230° at 8°/min temperature rise). Chromatography on Florisil gave in the petroleum ether fraction two components, whose vpc retention time corresponded to that of the first two peaks of the reduction mixture, compounds **11** and **12**. The infrared spectrum of this mixture showed only hydrocarbon peaks. The ultraviolet spectrum indicated the presence of an olefin showing λ_{max} at 267 nm.

After removal of the solvent, 2-methyl-2-phenylindan (**11**) was obtained as a colorless oil [3.3 g (15 mmol), 44.7%, calculation based on vpc ratio] and was distilled *in vacuo* (0.5 mm, 90°). Vpc retention time proved this compound to be the first peak.

Anal. Calcd for $C_{16}H_{16}$: C, 92.30; H, 7.69. Found: C, 92.28; H, 7.77.

Various methods were employed to effect the isolation of the second component, 2-methyl-3-phenylindene (**12**). Among these were fractional distillation as well as separation by vpc on an Apiezon L preparative column, all of which proved fruitless.

It was shown, however, by vapor phase chromatography that the olefin **12** obtained in this reduction mixture was not identical with 2-phenyl-3-methylindene (**13**) which was prepared independently, as shown by their different retention times. Thus, it is concluded that the olefin obtained in this reduction mixture is the other isomer, 2-methyl-3-phenylindene (**12**), as predicted by the proposed mechanism.[2]

The third component was obtained from the petroleum ether–benzene (1:1) eluate, and was identified as starting ketone 2-methyl-2-phenyl-1-indanone (**10**) [3.0 g (13 mmol), 40%, calculation based on vpc ratios].

Kinetic Studies in the Clemmensen Reduction of 2-Phenyl-1-indanone-2-d_1 (4) and 2-Phenyl-1-indanone (1).—The two reactions below were run under identical Clemmensen conditions.

To a solution of 0.5 g of mercuric chloride in 7.5 ml of D_2O (99.8% D) and 0.25 ml of DCl (38% in D_2O) there was added 5 g of granular zinc. After 15 min of stirring, the liquid was decanted and the amalgamated zinc was washed twice with D_2O. To this zinc amalgam there was added a solution of 2.5 g (11 mmol) of 2-phenyl-1-indanone-2-d_1 (**4**) in 20 ml of toluene, 3.5 ml of D_2O, and 22.5 ml of DCl.

The undeuterated ketone (**1**) was subjected to identical Clemmensen conditions at the same time.

Kinetic measurements were carried out by following the increase of the uv absorption of 2-phenylindene-3-d_1 (**6**) and 2-phenylindene (**4**), respectively, at 315 nm. Aliquots of 0.100 ml were taken from the reaction mixture at different times and diluted with methanol to obtain an optical density reading of 0.3–0.8; these readings were then converted to a common volume (50 ml).

The change of optical density (D) with time was measured. The first-order rate constants were calculated from the following equation.

$$K = \frac{1}{t} \ln \frac{D_\infty - D_0}{D_\infty - D}$$

$K_H = 6.490 \times 10^{-2}$ sec^{-1}; $K_D = 4.146 \times 10^{-2}$ sec^{-1}

A graph of log $(D_\infty - D_0)/(D_\infty - D)$ *vs.* time (see Figure 1) gave a straight line, indicating that the reaction is first order under these conditions. From the slopes of the lines K_H and K_D were obtained. K_H/K_D was found to be 1.53. This represents the average of four runs.

Registry No.—**4**, 39253-52-6; **5**, 39253-53-7; **6**, 39253-54-8; **7**, 39253-55-9; **8**, 39253-56-0; **10**, 10474-32-5; **11**, 39253-58-2.

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Modified Birch Reductions. Lithium in *n*-Alkylamines

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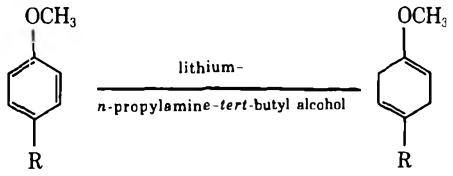
p-Methoxyanisole, *p*-methylanisole, *p*-*tert*-butylanisole, *N*,*N*-dimethyl-*p*-toluidine, and *N*,*N*,*N*′,*N*′-tetramethyl-*p*-phenylenediamine were reduced using lithium–*n*-propylamine–*tert*-butyl alcohol reagent. The anisoles gave results equivalent to the Birch (liquid ammonia) reductions while the anilines gave mainly the tetrahydro derivatives. In the reduction of *p*-di-*tert*-butylbenzene and *p*-dicyclohexylbenzene using lithium–ethylamine–ethyl alcohol the principal respective products were 1,4-di-*tert*-butyl-1,4-cyclohexadiene and 1,4-dicyclohexyl-1,4-cyclohexadiene. This procedure may provide a general approach for preparing many cyclohexadiene derivatives in good yield and purity, which have not been accessible by any simple methods described hitherto. Upon reduction of 2,3-dimethylnaphthalene with lithium–ethylamine–ethyl alcohol the tetrahydro derivative 2,3-dimethyl-1,4,5,8-tetrahydronaphthalene was formed as the major product. The reduction of *p*-di-*tert*-butylbenzene with lithium–ethylamine provided an improved synthesis of 1,4-di-*tert*-butylcyclohexene, while reduction of *p*-diisopropylbenzene afforded 1,4-diisopropylcyclohexene; 1,4-dicyclohexylcyclohexene and 1,4-dimethylcyclohexene were also prepared using lithium–ethylamine.

The Birch reduction of aromatic compounds to the corresponding dihydro compounds by use of alkali metals and alcohols in liquid ammonia is a very useful synthetic procedure. In laboratories where Birch reductions are not frequently run, the use of an alkylamine, such as ethyl- or *n*-propylamine, as the solvent would be safer and more convenient than liquid ammonia. Benkeser[1] has previously reported that the reduction of ethylbenzene, cumene, *tert*-butylbenzene, and anisole using lithium–methylamine–alcohol combinations gave yields comparable with those of the Birch reductions. The purpose of this work was to investigate the synthetic scope and limitations of reductions of para-substituted aromatics with lithium–alkylamine–alcohol combinations and lithium–alkylamine combinations.

Reduction of Para-Substituted Anisoles.—The results obtained on reduction of *p*-methoxyanisole (**1**), *p*-methylanisole (**3**), and *p*-*tert*-butylanisole (**5**) to the corresponding 1-methoxy-4-substituted 1,4-cyclohexadienes using lithium–*n*-propylamine–*tert*-butyl alcohol are summarized in Table I. Preliminary experiments on the reduction of **1** indicated that the concentration of lithium and the presence of alcohol were the most

(1) R. A. Benkeser, *et al.*, *J. Org. Chem.*, **28**, 1094 (1963). For a comprehensive treatment of Birch reductions and metal–amine reductions, several reviews on both theoretical and synthetic aspects exist in the literature: R. L. Augustine, "Reduction: Techniques and Applications in Organic Synthesis," Marcel Dekker, New York, N. Y., 1968; A. J. Birch, *Quart. Rev. (London)*, **4**, 69 (1950); A. J. Birch and H. Smith, *ibid.*, **12**, 17 (1958); H. Smith, "Organic Reactions in Liquid Ammonia," Vol. 1, part 2, Wiley, New York, N. Y., 1963; R. G. Harvey, *Synthesis* **4**, 161 (1970); A. J. Birch and G. Subba Rao, *Advan. Org. Chem.*, **8**, 1 (1971); E. M. Kaiser, *Synthesis*, **8**, 391 (1972).

TABLE I
REDUCTION OF PARA-SUBSTITUTED ANISOLES



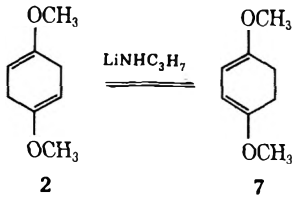
R	Anisole	Product	Yield, %	Birch redn yields, %
OCH_3	1	2	64	94[a]
CH_3	3	4	61[b]	33[c]
			64	70[d]
				80[e]
				45[f]
				80[g]
t-C_4H_9	5	6	49[h]	35[i]
				63[j]

[a] Reported in ref 3. [b] Ethyl alcohol used. [c] Isolated as 4-methyl-3-cyclohexen-1-one and 4-methyl-2-cyclohexen-1-one in ref 5. [d] Reported in ref 18. [e] Isolated as 4-methyl-3-cyclohexen-1-one by E. A. Braude, *et al.*, *J. Chem. Soc.*, 3228 (1958). [f] Isolated as 4-methyl-2-cyclohexen-1-one by W. G. Dauben, G. W. Shaffer, and N. D. Vietmeyer, *J. Org. Chem.*, **33**, 4060 (1968). [g] Isolated as the ethylene ketal of 4-methyl-3-cyclohexen-1-one by W. C. Agosta and W. L. Schreiber, *J. Amer. Chem. Soc.*, **93**, 3947 (1971). [h] Contaminated with 9% *p*-*tert*-butylphenol. [i] Reported by R. D. Stolow, *J. Org. Chem.*, **28**, 2862 (1963). [j] Reported in ref 19.

important variables. The amount of reduction was proportional to the amount of lithium used, and reductions without alcohol led to large quantities of 1,4-dimethoxy-1,3-cyclohexadiene (**7**, conjugated dihydro), rather than 1,4-dimethoxy-1,4-cyclohexadiene (**2**, unconjugated dihydro). The presence of **7** is attributed to the influence of the amide anion catalyzing the development of conjugation. Changes in the nature and/or concentration of the amine and of the alcohol, or some variation of the temperature, seemed to have little or no effect upon the course and extent of reductions.

The reduction of **5** presented some difficulties; a low boiling fraction was always present which was tentatively identified by nmr analysis as a mixture of isomeric *tert*-butylcyclohexenes. The product, 1-methoxy-4-*tert*-butyl-1,4-cyclohexadiene (**6**) was always contaminated with *p*-*tert*-butylphenol even after strong base washes. The hydrogenolysis of the methoxy moiety is quite common[2-4] and the demethylation of anisoles has been reported in both Birch (liquid ammonia) reductions[3,5] and lithium–amine reductions.[6]

The isomerization of **2** by refluxing for 1.5 hr with



2 **7**

lithium *n*-propylamide gave a mixture containing 69% **7** and 31% **2**. Birch[7] reports that 1,4-cyelohexadienes are equilibrated with the 1,3-dienes to the extent of 75–80% by strong bases such as potassium amide in liquid ammonia and potassium *tert*-butoxide in DMSO. Refluxing for 7.5 hr with lithium *n*-propylamide gave a complex mixture of the compounds **1**, **2**, and **7**. Birch[3,4] previously reported that dihydroanisoles undergo dehydrogenation when subjected for longer periods of time to reaction conditions which can effect conjugation.

Reduction of *N*,*N*-Dimethylanilines.—*N*,*N*-Dimethyl-*p*-toluidine (**8**) was treated with lithium–*n*-propylamine–*tert*-butyl alcohol, and the crude product was hydrolyzed to give a low yield (21%) of ketonic product. On the basis of glc analysis this consisted of ~90% 4-methylcyclohexanone (**9**) and 10% 4-methyl-3-cyclohexenone (**10**). Another reduction of **8** was attempted using one half the lithium used previously. The reduction was incomplete as evidenced by the presence of **8**, identified by the nmr and ir spectra of the crude product. Hydrolysis of crude product gave a low yield (24%) of ketone[8] which contained 65% **9** and 35% **10** (Scheme I).

The reduction of *N*,*N*,*N*′,*N*′-tetramethyl-*p*-phenylenediamine with lithium–*n*-propylamine–*tert*-butyl alcohol was carried out using the diminished quantity of lithium. The aromatic amine was not completely reduced as evidenced by the ir spectrum of the crude product. This was hydrolyzed and converted to the dioxime of 1,4-cyclohexanedione in very low yield (1.7%).[9]

The Birch reductions of *N*,*N*-dimethylanilines using lithium and *tert*-butyl or *tert*-amyl alcohol are superior to lithium–amine–alcohol combinations, giving products which contain no more than 5% tetrahydro derivatives.[7] Stork[10] found, however, that the use of ethanol in the reductions of *N*,*N*-dimethylanilines gave higher proportions (34–47%) of tetrahydro products.

Krapcho and Bothner-By[11] previously reported that *p*-di-*tert*-butylbenzene (**11**) with lithium–ammonia–ethyl alcohol experienced no reduction reaction. The reduction of **11** with lithium–ethylamine–ethyl alcohol has now been realized; a product mixture containing 86% 1,4-di-*tert*-butyl-1,4-cyclohexadiene (**12**) and 14% 1,4-di-*tert*-butylcyclohexene (**15**) has been obtained in good yield. Purification gave **12** in 56% overall yield. This procedure may possibly provide a general approach for preparing cyclohexadiene derivatives in good yield and purity. Using lithium–*n*-propylamine–ethyl alcohol afforded a mixture containing 55% **11**, 43% **12**, and 2% **15**. Using the lithium–ethylamine–ethyl alcohol reagent, *p*-dicyclohexylbenzene (**13**) was reduced to 1,4-dicyclohexyl-1,4-cyclohexadiene (**14**) in 73% yield (Table II).

The Stolow and Ward[12] synthesis of **15** from **11**, using lithium in refluxing ethylenediamine has frequently

(2) A. J. Birch, P. Hextall, and S. Sternhell, *Aust. J. Chem.*, **7**, 256 (1954).
(3) A. J. Birch, *J. Chem. Soc.*, 102 (1947).
(4) A. J. Birch and G. S. R. Subba Rao, *Aust. J. Chem.*, **23**, 1641 (1970).
(5) A. J. Birch, *J. Chem. Soc.*, 430 (1944).
(6) L. Reggel, R. A. Friedel, and I. Wender, *J. Org. Chem.*, **22**, 891 (1957).
(7) A. J. Birch, *et al.*, *J. Chem. Soc. C*, 637 (1971).

(8) Analysis of ketones does not take into account a tetrahydro product such as 4-dimethylamino-1-methylcyclohexene or the isomeric hexahydro products *cis*- and *trans*-1-dimethylamino-4-methylcyclohexane, because, being amines, they are removed during hydrolysis.
(9) In this reduction, starting material or tetrahydro or hexahydro products would be removed as salts during hydrolysis.
(10) G. Stork and W. N. White, *J. Amer. Chem. Soc.*, **78**, 4604 (1956).
(11) A. P. Krapcho and A. A. Bothner-By, *J. Amer. Chem. Soc.*, **81**, 3658 (1959).
(12) R. D. Stolow and R. A. Ward, *J. Org. Chem.*, **31**, 965 (1966).

SCHEME I

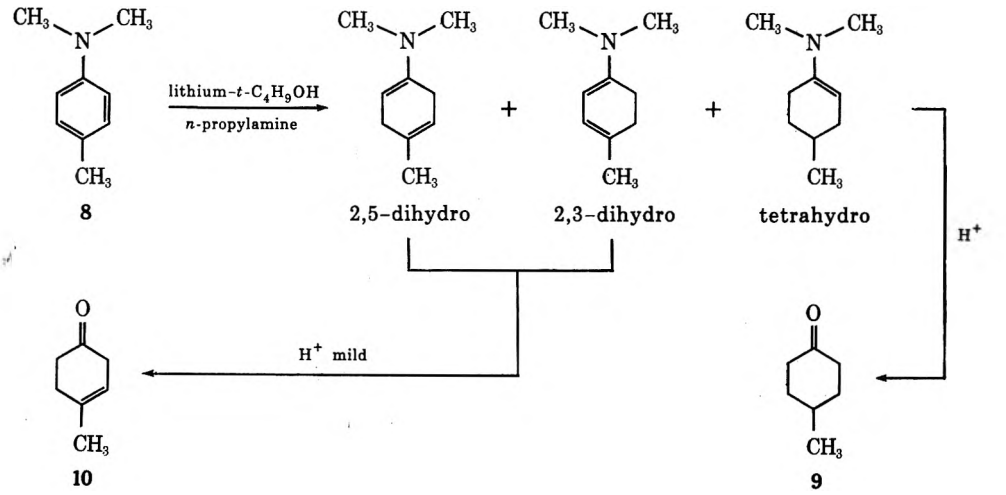
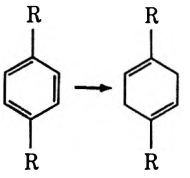


TABLE II

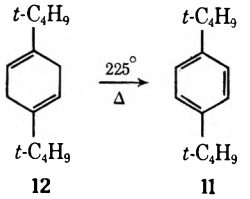
REDUCTION OF *p*-DIALKYLBENZENES



R	Alkylbenzene	Cyclohexadiene	Yield, %
Lithium–Ethylamine–Ethyl Alcohol Reagent			
tert-C_4H_9	11	12	56
c-C_6H_{11}	13	14	73[a]
Lithium–Ethylamine			
t-C_4H_9	11	15	74
c-C_6H_{11}	13	16	76
i-C_3H_7	17	18	92
CH_3	19	20	60

[a] Nmr showed 4% starting material.

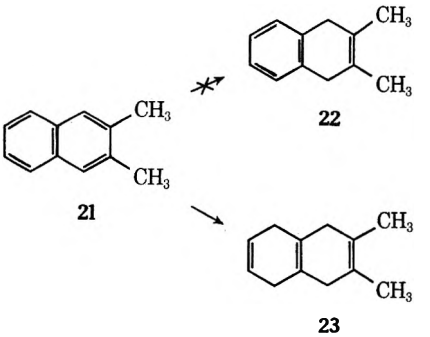
been cited as an example of lithium–amine reductions. However, their total yield of contaminated **15** was 44%, and this material contained 12% starting compound. Lithium in ethylamine at 0° gave rise to pure **15** in 74% yield. This reduction of **11** to **15**, as in the previous preparation of **12**, appeared to afford high yields only with ethylamine. Reduction of **11** with lithium–*n*-propylamine gave a crude reaction mixture containing 16% **15** and 84% **11**.



The difference between lithium in ethylamine and lithium in refluxing ethylenediamine is due to the fact that *N*-lithioethylenediamine ($LiNHCH_2CH_2NH_2$), a product of the reduction reaction, is a powerful dehydrogenating reagent capable of converting dihydrobenzenes to aromatics.[13] The intermediate **12** may be further reduced to **15** or be dehydrogenated to **11** with *N*-lithioethylenediamine in refluxing ethylenediamine.

Moreover, in an attempt to use glc for analysis, a sample containing **12** was subjected to an injection port temperature of 255° and was partially dehydrogenated to **11**.[14] The lithium–ethylamine reagent was also used with *p*-dicyclohexylbenzene (**13**), *p*-diisopropylbenzene (**17**), and *p*-xylene (**19**) to show the scope of this reaction.

Reduction of 2,3-Dimethylnaphthalene.—In an attempt to obtain **22**, 2,3-dimethylnaphthalene (**21**) was reduced using the lithium–ethylamine–ethyl alcohol reagent. Because of the greater reactivity of naphthalenes in reductions, a smaller excess of lithium was used compared with that used in the reduction of **11** to **12**. Analysis of the reaction product showed that reduction had gone beyond the dihydro state to the tetrahydro compound yielding a mixture of ~82% **23** and 18% **21**. Increasing the amount of lithium to a slight stoichimetric excess for reduction to the tetrahydro state gave pure **23** in 72% yield. This product was readily identified by the simplicity of its nmr spectra arising from its highly symmetrical structure.



(13) L. F. Fieser and M. Fieser, "Reagents of Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1967.

(14) There have been studies in recent literature on pyrolysis of 1,4-cyclohexadiene to benzene. See references cited in R. B. Woodward and R. Hoffman, "The Conservation of Orbital Symmetry," Verlag Chemie Academic Press, Germany, 1970.

Experimental Section[15]

General Procedure for Reduction Using Lithium–Amine–Alcohol.—A three-necked, oven-dried, 500-ml round-bottom flask equipped with thermometer, magnetic stirrer, and Dry Ice condenser was used for all reductions. The flask was cooled in an ice bath, and the aromatic substrate, the amine, and the first portion of alcohol were added. The alcohol and lithium were usually added in three portions. The alcohol was always added before the lithium and was always in slight excess. The lithium was cut into small pieces and washed with petroleum ether (bp 40–60°). The lithium was added when the flask cooled to 0° and was allowed to react completely before the next portion of alcohol and lithium was added. The total reaction time after the first lithium addition was usually 5–6 hr. The *n*-propylamine was then distilled off or the ethylamine evaporated using a steam bath. The flask was then cooled and 200 ml of ice–water and 300 ml ether were added. The aqueous layer was extracted with two 150-ml portions of ether. The combined ether layers were washed with two 100-ml portions of water and dried over magnesium sulfate. The ether solution was then rotary evaporated to the crude product.

Reductions Using Lithium–Ethylamine.—These used 146 ml (100 g) of ethylamine and the lithium was added in two portions. About 3 hr after the first lithium addition, the dark blue color faded. After an additional 3.5 hr, an excess of ethanol was added and the ethylamine allowed to evaporate.

1,4-Dimethoxy-1,4-cyclohexadiene (2).—A solution of 13.5 g (0.098 mol) of 1,4-dimethoxybenzene (1) (Aldrich) in 225 ml of *n*-propylamine was reduced by 39.8 g (0.537 mol) of *tert*-butyl alcohol and 3.60 g (0.523 g-atom, 40 cm) of lithium. Evaporation of the ether solution gave a dark red oil which solidified upon cooling. The crude solid was dissolved in 50 ml of petroleum ether (bp 40–60°) and this solution was passed through a short column of neutral alumina. The clear petroleum ether solution was evaporated on a steam bath to a clear liquid which solidified upon cooling. The white crystals were filtered and dried to give 8.8 g (64%) of pure 2: mp 51–53° (lit.[3] mp 54°); nmr δ 2.73 (m, 4 H), 3.48 (s, 6 H), 4.47 (m, 2 H); ir (Nujol) 1675 (s), 1220 (s), 1180 (s), 1040 (s), 780 (s), 700 cm^{-1} (s); mol wt (mass spectrum) 140.

For further identification a suspension of 4.0 g (0.028 mol) of 2 and 25 ml of 10% HCl was heated on a steam bath for 1 hr. The reaction mixture was extracted with two 25-ml portions of $CHCl_3$ and the $CHCl_3$ was evaporated on a steam bath. A yellow oil was obtained which solidified upon cooling. Recrystallization from 10 ml of absolute EtOH gave 0.7 g (23%) of white 1,4-cyclohexanedione: mp 76–78° (lit.[3] mp 78°); nmr δ 2.62 (s); ir (Nujol) 1700 (s), 1130 (s), 960 (s), 700 cm^{-1} (s). Conversion of the dione to the dioxime[16] gave white crystals: mp 195–196° (lit.[17] mp 188°); ir (Nujol) 3300–3300 (s), 1650 cm^{-1} (s).

1-Methoxy-4-methyl-1,4-cyclohexadiene (4). A. *tert*-Butyl Alcohol.—Following the previously described procedure, 12.0 g (0.098 mol) of *p*-methylanisile (3) (Aldrich) was reduced. Distillation of the light yellow-brown crude material gave 7.8 g (64%) of clear, sweet-smelling 4: bp 56–57° (9 mm) [lit.[4] bp 80° (20 mm)]; nmr δ 1.65 (s, 3 H), 2.63 (m, 4 H), 3.45 (s, 3 H), 4.48 (m, 1 H), 5.27 (m, 1 H); ir (neat) 1700 (m), 1675 (s), 1220 (s), 1180 (s), 780 (s), 700 cm^{-1} (s); mol wt (mass spectrum) 124. Nmr and ir data correlate with literature values.[4]

B. Ethyl Alcohol.—This reduction was carried out exactly as above using 24.0 g (0.537 mol) of ethyl alcohol instead of *tert*-butyl alcohol. Distillation gave 7.4 g (61%) of 4, bp 56° (9 mm). Following the procedure of Birch,[18] 4 was converted to an authentic sample of 4-methyl-3-cyclohexenone (10) (crude ketone): nmr δ 1.77 (s, 3 H), 2.40 (s, 4 H), 2.75 (m, 2 H), 5.43 (m, 1 H); ir (neat) 1700 (vs), 1190 (s), 1050 (s), 770 cm^{-1} (s); vpc R_t 14.25 min on a 12 ft × 0.25 in. 10% silicone on Chromosorb W column at 85° with He flow rate of 78 ml/min and He pressure of 62 psi. Glc analysis showed the product to contain ~5% 4-methylcyclohexanone (9). Retention time and peak enhancement were used to identify 9.

1-Methoxy-4-*tert*-Butyl-1,4-cyclohexadiene (6).—A solution of 16.1 g (0.098 mol) of *p-tert*-butylanisole (5) was reduced using 3.1 g (0.457 g-atom) of lithium and 36.5 g (0.475 mol) of *tert*-butyl alcohol. Distillation gave two fractions. The first fraction, 1.7 g, bp 56–58° (8 mm), was shown by nmr analysis to contain a small amount of 6 with the isomeric *tert*-butylcyclohexenes as major product. The isomeric *tert*-butylcyclohexenes were tentatively identified by absorptions attributed to them in the nmr at δ 0.88 (s), 1.33–2.25 (br m), 5.45 (m), 5.68 (m). The second fraction consisted of 8.6 g (49%) of 6: bp 92° (8 mm) [lit.[15] bp 43° (0.4 mm)]; nmr δ 1.05 (s, 9 H), 2.72 (m, 4 H), 3.48 (s, 3 H), 4.53 (m, 1 H), 5.43 (m, 1 H); ir (neat) 1675 (m), 1650 (m), 1220 (s), 1180 (s), 790 cm^{-1} (s); mol wt (mass spectrum) 166. Nmr analysis showed the presence of 9% *p-tert*-butylphenol. The *p-tert*-butylphenol was further identified in an orientation experiment where it was extracted from the distillation residue. The nmr and ir spectra of the crude extract matched perfectly with authentic spectra of *p-tert*-butylphenol. The crude phenol and an authentic sample of *p-tert*-butylphenol were converted into its benzoate: mp (crude extract) 81–82° (lit.[20] mp 82°); mp (authentic) 81.5–82.0°; mmp 81–82°. Ir spectra of the benzoates matched perfectly. In some runs, the conjugated diene, 1-methoxy-4-*tert*-butyl-1,3-cyclohexadiene, was observed and identified from its nmr: nmr δ 1.05 (s, 9 H), 2.17 (s, 4 H), 3.45 (s, 3 H), 4.78 (d, 1 H, J = 7 Hz), 5.40 (d, 1 H, J = 7 Hz).

Reduction of *N,N*-Dimethyl-*p*-toluidine (8). A.—A solution of 13.3 g (0.098 mol) of *N,N*-dimethyl-*p*-toluidine (8) (Eastman White Label) in 225 ml of *n*-propylamine was reduced with 39.8 g (0.537 mol) of *tert*-butyl alcohol and 3.60 g (0.523 g-atom, 40 cm) of lithium. Petroleum ether (bp 40–60°) was used for extraction. The crude reduction product was hydrolyzed by stirring with 100 ml of 1 *N* HCl. Distillation of the crude ketone gave three fractions, bp 73–75° (25 mm), totaling 3.3 g. To identify the ketone, a 2,4-dinitrophenylhydrazone (DNPH)[16] was made using 0.5 g of the middle fraction. The crude orange solid had mp 130–135° (unclear melt). (The literature reports the following values. DNPH of 4-methyl-3-cyclohexenone: orange,[18] mp 120–121°; orange,[21] mp 131–134°; orange,[7] mp 128–129°. DNPH of 4-methylcyclohexanone: orange,[21] mp 133–134°.) In the effort to differentiate between the saturated and unsaturated ketone by effecting acid-catalyzed conjugation of the DNPH, a small amount was heated with 1 drop of concentrated H_2SO_4 in EtOH for a few minutes. The orange product of this reaction had mp 128–130°. (The literature reports the following values. DNPH of 4-methyl-2-cyclohexenone: crimson,[18] mp 173–174°; crimson,[21] mp 172–175°.)

Glc analysis (Table III) of the distillation fractions of a 12 ft × 0.25 in. 10% silicone on Chromosorb W column at 85° showed the first fraction to contain 90% 4-methylcyclohexenone (9) and 10% 4-methyl-3-cyclohexenone (10), while the third fraction contained 87% 9 and 13% 10. Identification was made by comparison of

TABLE III

GLC ANALYSIS (10% SILICONE ON CHROMOSORB W AT 85°)

Fraction	4-Methylcyclohexanone, %	4-Methyl-3-cyclohexenone, %
1	71	29
2	65	35
	62 (nmr)	38 (nmr)
3	63	37

(15) Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer with polystyrene calibration at 1601 cm^{-1}. Absorption bands are reported in reciprocal centimeters and intensities are reported as vs (very strong), s (strong), m (medium), and w (weak). Nmr spectra was recorded on a Varian Model A-60 spectrometer in carbon tetrachloride with tetramethylsilane (TMS) as the internal standard. The chemical shifts are reported in parts per million (δ). Mass spectra were recorded on a CEC Model 21-110 B double focusing spectrometer. Vapor phase chromatography was performed on a F & M Model 200 chromatograph with thermal conductivity detector. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich. All boiling points and melting points are uncorrected. Melting points were determined on a Mel-Temp apparatus. The *n*-propylamine and ethylamine were Eastman Kodak White Label grade. The *n*-propylamine was purified by stirring over sodium for 1 or 2 days and then distilling from the mixture. The lithium was obtained from Foote Mineral Co. in the form of ribbon (0.089 g/cm) in petrolatum.

(16) R. Shriner, R. Fuson, and D. Curtin, "The Systematic Identification of Organic Compounds," Wiley, New York, N. Y., 1964.

(17) Beilstein reports the melting point of the dioxime at 188°, but also reports that quick heating gives a melting point of 200° and slow heating a melting point of 192° with slight decomposition.

(18) A. J. Birch, *J. Chem. Soc.*, 593 (1946).

(19) D. A. Bolon, *J. Org. Chem.*, **35**, 715 (1970).

(20) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1966.

(21) B. B. Millward, *J. Chem. Soc.*, 26 (1960).

retention times and peak enhancement with those of authentic ketones. An authentic sample of **9** was prepared according to literature:[22] bp 169–170° (lit.[22] bp 168–170°); nmr δ 0.95 (d, 3 H), 1.00–2.00 (br, 5 H), 2.10 (m, 4 H); ir (neat) 1710 cm^{-1} (vs); glc R_t 12.25 min on a 12 ft × 0.25 in. 10% silicone on Chromosorb W column at 85° with He flow rate of 78 ml/min and He pressure of 62 psi.

B.—Using 2.03 g (0.294 g-atom, 22.5 cm) of lithium and 22.9 g (0.309 mol) of *tert*-butyl alcohol, 13.3 g (0.098 mol) of **8** was reduced. The crude reduction product was hydrolyzed by stirring for 1 hr with 5.1 g (0.041 mol) of oxalic acid and in 40 ml of H_2O. Ir and nmr spectra of the crude ketone product showed the presence of **8**. Removal of **8** by acid washes and distillation gave three clear fractions: (1) 0.3 g, bp 75–76° (25 mm); (2) 1.7 g, bp 76–77° (25 mm); (3) 0.6 g, bp 65–70° (20 mm).

Reduction of *N,N,N',N'*-Tetramethyl-*p*-phenylenediamine.—A solution of 12.7 g (0.098 mol) of *N,N,N',N'*-tetramethyl-*p*-phenylenediamine[23] in 200 ml of *n*-propylamine was reduced with 13.0 g (0.175 mol) of *tert*-butyl alcohol and 1.14 g (0.166 g-atom, 6.4 cm) of lithium. A dark red oil was obtained after petroleum ether extraction and evaporation. The ir spectrum indicated the presence of some starting material. Hydrolysis of the crude product with 50 ml of 10% HCl followed by $CHCl_3$ extraction gave 2.5 g of a dark red-black liquid which showed presence of carbonyl in the ir at 1700 cm^{-1}. Conversion of this material to its dioxime afforded a dark red-black gummy solid which could not be recrystallized. The filtrate from the dioxime preparation yielded, after sitting for 2 days, 0.5 g of dark brown crystals, mp 192–203°. The crystals were recrystallized from 95% EtOH to give 0.2 g of dioxime (1.7% from tetramethyl): mp 194–198° (lit[17] mp 188°); ir (Nujol) 3300–3000 (s), 1650 cm^{-1} (s) (the ir spectrum matches the spectrum of authentic 1,4-cyclohexanedione dioxime).

1,4-Di-*tert*-butyl-1,4-cyclohexadiene (12).—A solution of 12.4 g (0.066 mol) of *p*-di-*tert*-butylbenzene (**11**) in 146 ml (100 g) of anhydrous ethylamine was reduced with 16.4 g (0.356 mol) of EtOH and 2.12 g (0.308 g-atom, 23.3 cm) of lithium. The crude product was recrystallized from MeOH to give 10.1 g of white crystals: mp 53–56°; nmr analysis, 86% diolefin, 14% monoolefin. This material was recrystallized twice more from MeOH to give 7.1 g (56%) of white fluffy crystals of **12**: mp 61.5–62.5°; nmr δ 1.03 (s, 18 H), 2.67 (m, 4 H), 5.48 (m, 2 H) (no monoolefin present); ir (Nujol) 1310 (w), 1270 (w), 1040 (m), 950 (m), 800 cm^{-1} (m); mol wt (mass spectrum) 192.

Anal. Calcd for $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: C, 87.52; H, 12.38.

The *p*-di-*tert*-butylbenzene (**11**) was prepared according to the literature.[24] Two recrystallizations gave white crystals: mp 75–77° (lit.[24] mp 78°); nmr δ 1.32 (s, 18 H), 7.23 (s, 4 H); ir (Nujol) 1500 (w), 1250 (w), 1120 (w), 1010 (2), cm^{-1} 820 (s).

1,4-Dicyclohexyl-1,4-cyclohexadiene (14).—In a procedure analogous to the preparation of **12**, 12.0 g (0.050 mol) of *p*-dicyclohexylbenzene (**13**) in 146 ml (100 g) of anhydrous ethylamine was reduced by 1.6 g (0.231 g-atom) 17.5 cm) of lithium and 12.3 g (0.265 mol) of ethanol. The crude product was recrystallized from absolute ethyl alcohol to give 10.7 g of white solid, mp 88.5–90.5°. Nmr analysis indicated the composition of this material to be 79% **14** and 21% **13**. Four recrystallizations from ethyl alcohol gave 8.9 g (73%) of white flakes (nmr analysis showed 4% starting material): mp 91.0–92.5°, nmr δ 0.83–2.33 (br m, 22 H), 2.60 (m, 4 H), 5.38 (m, 2 H); ir (Nujol) 950 (m), 880 (w), 850 (w), 800 cm^{-1} (w); mol wt (mass spectrum) 244.

Anal. Calcd for $C_{18}H_{28}$: C, 88.46; H, 11.54. Found: C, 88.37; H, 11.62.

1,4-Di-*tert*-butylcyclohexene (15).—Reduction of 12.4 g (0.066 mol) of *p*-di-*tert*-butylbenzene (**11**) in 146 ml (100 g) of ethylamine required 2.70 g (0.392 g-atom, 30 cm) of lithium. Recrystallization from MeOH gave 9.4 g (74%): mp 54.0–55.0° (lit.[12] mp 54.0–54.5°); nmr δ 0.88 (s, 9 H), 1.02 (s, 9 H), 1.02–2.38 (br m, 7 H), 5.42 (m, 1 H); ir (Nujol) 1240 (w), 1030 (w), 830 (w), 805 cm^{-1} (w); mol wt (mass spectrum) 194; glc R_t 5.5 min on a 6 ft × 0.25 in. 10% Carbowax on Chromosorb W column at 175° with He flow rate of 78 ml/min and He pressure of 62 psi.

1,4-Dicyclohexylcyclohexene (16).—This compound was prepared in an analogous manner to the preparation of **15**. The only change in procedure was that the 16.0 g (0.066 mol) of *p*-dicyclohexylbenzene (**13**) was dissolved in 292 ml (200 g) of anhydrous ethylamine owing to lack of solubility. The crude product was recrystallized from an ethyl alcohol–methyl alcohol mixture to give 12.3 g (76%) of white crystals, mp 107–108°. Nmr analysis showed no starting material. An analytical sample was recrystallized from ethyl alcohol: mp 107° (lit.[25] mp 111–113°); nmr δ 0.78–2.33 (br, m, 29 H), 5.35 (m, 1 H); ir (Nujol) 900 (w), 890 cm^{-1} (w); mol wt (mass spectrum) 246.

Anal. Calcd for $C_{18}H_{30}$: C, 87.73; H, 12.27. Found: C, 87.60; H, 12.55.

1,4-Diisopropylcyclohexene (18).—A solution of 15.9 g (0.098 mol) of *p*-diisopropylbenzene (**17**) (Aldrich) in 146 ml (100 g) ethylamine was reduced with 4.05 g (0.588 g-atom, 45 cm) of lithium. Distillation gave 14.9 g (92%) of clear **18**: bp 92° (20 mm); $n^{24}D$ 1.4584; nmr δ 0.88 (d, 6 H), 0.97 (d, 6 H) (doublets are overlapping for isopropyl groups), 1.02–2.50 (br, m, 9 H), 5.31 (br, m, 1 H); ir (neat) 2900–2800 (vs), 1460 (s), 1380 (s), 1360 (s), 810 cm^{-1} (m); mol wt (mass spectrum) 166.

Anal. Calcd for $C_{12}H_{12}$: C, 86.66; H, 13.34. Found: C, 86.43; H, 13.46.

1,4-Dimethylcyclohexene (20).—The reduction of 13.3 g (0.125 mol) of *p*-xylene (**19**) (Eastman) in 146 ml (100 g) ethylamine required 5.2 g (0.755 g-atom, 57.6 cm) of lithium. Distillation gave 6.5 g (60%) of **20**: bp 112–113° (lit.[26] bp 124–126°); $n^{24}D$ 1.4448 (lit.[26] ($n^{24}D$ 1.4457); nmr δ 0.95 (d, 3 H) 1.03–250 (br m with strong s at 1.61, 10 H), 5.38 (br m, 1 H); ir (neat) 2900 (s), 1460 (s), 1380 (s), 1040 (m), 890 (m), 790 (m), 780 cm^{-1} (m).

Reduction of 2,3-Dimethylnaphthalene (21). A. A solution of 13.0 g (0.083 mol) of **21** in 146 ml (100 g) of ethylamine was reduced by 11.3 g (0.266 mol) ethyl alcohol and 1.79 g (0.261 g-atom, 20 cm) of lithium. Recrystallization from MeOH gave 9.6 g of white crystals: mp 64–70°; nmr analysis, 82% 2,3-dimethyl-1-4,5,8-tetrahydronaphthalene (**23**), 18% **21**.

B. Same as above except 17.1 g (0.370 mol) ethyl alcohol and 2.47 g (0.360 g-atom, 27.5 cm) of lithium were used. Recrystallization from ethyl alcohol gave 9.6 g (72%) of pure **23**: mp 67–69°; nmr δ 1.67 (s, 6 H), 2.43 (s, 4 H), 2.51 (s, 4 H), 5.70 (s, 2 H); ir (Nujol) 1380 (m), 1060 (w), 960 (w), 940 cm^{-1} (w); mol wt (mass spectrum) 160.

Anal. Calcd for $C_{12}H_{16}$: C, 89.92; H, 10.08. Found: C, 90.04; H, 10.03.

Dehydrogenation of 1,4-Di-*tert*-butyl-1,4-cyclohexadiene (12). A.—A solution of *N*-lithioethylenediamine was prepared under N_2 from 0.6 g (0.087 g-atom) of lithium and 35 ml of anhydrous ethylenediamine (distilled over sodium). A solution of 2.0 g (0.10 mol) of **12** in 65 ml of ethylenediamine was added and refluxed for 3 hr. Recrystallization of the crude product from MeOH gave 1.6 g (81%) of *p*-di-*tert*-butylbenzene (**11**): mp 75–77°; mmp 75–78° (no depression); nmr and ir spectrum matched those of authentic *p*-di-*tert*-butylbenzene.

B.—A sample of **12** which nmr analysis showed to contain 14% **15** was injected on the glc column with an injection port temperature of 255°. The chromatograph showed the product to contain 77% **12** (R_t 9.0 min), 13% **15** (R_t 5.5 min), and 10% **11** (R_t 10.5 min). Identity of the products was checked by peak enhancement and retention time. The glc was performed on a 6 ft × 0.25 in. 10% Carbowax on Chromosorb W column at 175° with He flow rate of 81 ml/min and He pressure of 62 psi.

Isomerization of 1,4-Dimethoxy-1,4-cyclohexadiene (2). A.—A solution of lithium *n*-propylamide was prepared by refluxing 0.36 g (0.052 g-atom) of lithium and 70 ml of *n*-propylamine for 4 days. A solution of 5.8 g (0.041 mol) of **2** in 40 ml of *n*-propylamine was added and refluxed for 1.5 hr under conditions which scrupulously excluded moisture and guaranteed an excess of base in solution throughout the isomerization. Nmr analysis of the crude product showed it to be 69% **7** [nmr 2.28 (s, 4 H), 3.48 (s, 6 H), 4.73 (s, 3 H)] and 31% **2**.

B.—Lithium *n*-propylamide was prepared from 0.73 g (0.105 g-atom) of lithium and 100 ml of *n*-propylamine by refluxing for 4 days. A solution of 12.3 g (0.088 mol) of **2** in 50 ml of *n*-propylamine was added and refluxed for 7.5 hr. Distillation gave two fractions: (1) 2.4 g, bp 31–58° (7 mm); (2) 5.6 g, bp

(22) M. Pezold and R. L. Shriner, *J. Amer. Chem. Socl*, **54**, 4707 (1932).

(23) J. R. Cox, Jr., and B. D. Smith, *J. Org. Chem.*, **29**, 488 (1964).

(24) J. A. Moore and D. L. Dalrymple, "Experimental Methods in Organic Chemistry," W. B. Saunders Co., Philadelphia, Pa., 1971, Chapter 15.

(25) J. V. Braun, G. Irmisch, and J. Nelles, *Ber.*, 1471 (1933).

(26) "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1965.

78–74° (7 mm). Nmr analysis showed the first fraction to contain 76% anisole, 17% **7**, and 7% **2**, while the second fraction contained 51% **7**, 18% **2**, 11% **1**, and 10% anisole. Anisole was identified by comparison with the nmr spectrum of an authentic sample and by conversion into its sulfonamide derivative: mp (isolated) 109–110.5°; mp (authentic) 111.5–112° (lit.[20] mp 111°); mmp 111–112.5° (no depression); ir spectra of sulfonamides matched perfectly.

Registry No.—**1**, 150-78-7; **2**, 39000-58-3; **3**, 104-93-8; **4**, 20023-36-3; **5**, 5396-38-3; **6**, 22566-53-6; **7**, 39000-61-8; **8**, 99-97-8; **9**, 589-92-4; **10**, 5259-65-4; **11**, 1012-72-2; **12**, 39000-62-9; **13**, 1087-02-1; **14**, 39000-63-0; **15**, 5009-02-9; **16**, 39000-65-2; **17**, 100-18-5; **18**, 39000-66-3; **19**, 106-42-3; **20**, 2808-79-9; **21**, 581-40-8; **23**, 39000-67-4; 1-methoxy-4-*tert*-butyl-1,3-cyclohexadiene, 37720-49-3; lithium, 7439-93-2.

Acknowledgment.—We are grateful to Dr. J. A. Moore, Dr. S. S. Kulp, Dr. H. Omura, L. A. Conley, and D. Viola for many services rendered during the course of the work.

Synthesis of *tert*-Carboxylic Acids from Olefins and Carbon Monoxide by Copper(I) Carbonyl Catalyst

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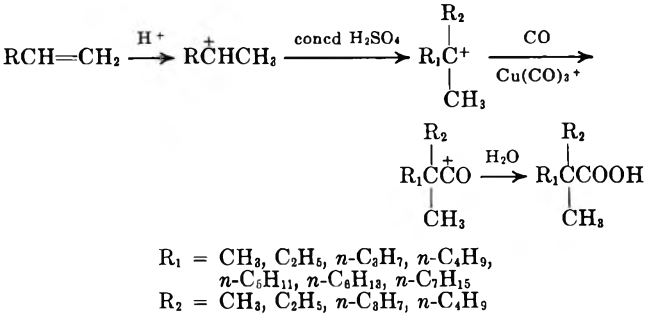
The new carbonylation reaction was proposed using Cu(I) carbonyl catalyst in concentrated H_2SO_4. In concentrated H_2SO_4 containing Cu(I) compound, olefins react with carbon monoxide at room temperature and atmospheric pressure to produce *tert*-carboxylic acids in high yields. Neither primary nor secondary carboxylic acids were found. The catalyst was prepared in concentrated H_2SO_4 from Cu(I) compounds and carbon monoxide. The amount of the Cu(I) compound sufficient for carrying out these carbonylation was as small as 0.2 mol/l. It is assumed that unstable Cu(I) tricarbonyl $[Cu(CO)_3^+]$ is transiently formed in concentrated H_2SO_4. The yields of the *tert*-carboxylic acids are as follows: *tert*-C_7 acid, 72% from 1-hexene; *tert*-C_8 acid, 82% from 1-heptene; *tert*-C_9 acid, 94% from 1-octene; and *tert*-C_{11} acid, 97% from 1-decene. Reaction optimum temperature was 20–50° for the monoolefins. The yield and reaction rate decreased with the decrease of H_2SO_4 concentration. At the H_2SO_4 concentrations less than 80%, no carboxylic acids were obtained.

Much work has been published concerning the carbonylation of olefin with carbon monoxide. Reppe[1] and others[2] reported the reaction catalyzed by metal carbonyls, and mixtures of *n*-carboxylic acid and *sec*-carboxylic acid were obtained. This reaction proceeds at high temperature and high pressure. On the other hand, Koch[3] and others[4,5] obtained branched carboxylic acids by the carbonylation of olefins in strong acid such as H_2SO_4, HF, H_3PO_4, or $BF_3 \cdot H_2O$. However, metal catalysts were not used in Koch type reaction. All these reactions need high carbon monoxide pressures.

Recently we found that Cu(I) carbonyl was easily formed from Cu(I) compounds and carbon monoxide in concentrated H_2SO_4.[6] Cu(I) carbonyl has high catalytic activity in the carbonylation of alcohols to carboxylic acids at room temperature and atmospheric pressure.[7]

$$ROH \xrightarrow{H_2SO_4} R'^+ \xrightarrow[Cu(CO)_3^+]{CO} R'CO^+ \xrightarrow{H_2O} t\text{-}R'COOH$$

This paper describes the synthesis of *tert*-carboxylic acids, from olefins and carbon monoxide, catalyzed by Cu(I) carbonyl in concentrated H_2SO_4. From various types of olefins, *tert*-carboxylic acids are generally formed by the isomerization of the intermediate carbonium ion in concentrated H_2SO_4. The reactions



using Cu(I) carbonyl catalyst provide new examples of the wide-ranging synthetic utility for carbonylation reactions.

Results and Discussion

The results of *tert*-carboxylic acid synthesis catalyzed by Cu(I) carbonyl from olefin and carbon monoxide are shown in Table I. Various kinds of olefins (terminal or internal olefins) gave *tert*-carboxylic acids in concentrated H_2SO_4. This is due to the isomerization of the carbonium ion intermediate prior to the carbonylation. Primary or secondary carboxylic acids were not found.

Cuprous oxide and cuprous sulfate were used as the Cu(I) compounds. The effect of the amount of cuprous oxide is illustrated in Figure 1. Without cuprous oxide, the rate of reaction was very slow, and the yield of carboxylic acid was less than 10%. When cuprous oxide was added in concentrated H_2SO_4, the rate of reaction increased considerably. The reaction was almost complete in 1–2 hr, and *tert*-carboxylic acids were obtained in high yields. On the other hand, Cu(II) compounds do not exhibit any catalytic activity.

(1) W. Reppe and H. Kröper, *Justus Liebigs Ann. Chem.*, **582**, 38 (1953).
(2) B. E. Kuvaev, N. S. Imyanitov, and D. M. Rudkovskii, *Karbonilirovanie Nenasyshchennykh Uglevodorodov*, 232 (1968); *Chem. Abstr.*, **71**, 21649z (1968).
(3) H. Koch, *Brennst. Chem.*, **36**, 321 (1955).
(4) K. E. Möller, *ibid.*, **45**, 129 (1964); Y. T. Eidus, K. V. Puzitskii, and S. D. Pirozhkov, *Neftekhimiya*, **8** (3), 343 (1968).
(5) S. Pawlenko, U. S. Patent 3,349,107 (1967); *Chem. Abstr.*, **68**, pc21540v (1967).
(6) Y. Souma and H. Sano, *Nihon Kagaku Zasshi*, **91**, 625 (1970).
(7) Y. Souma and H. Sano, *Kogyo Kagaku Zasshi*, **73**, 2723 (1970).

TABLE I

tert-CARBOXYLIC ACIDS DERIVED FROM OLEFINS AND CARBON MONOXIDE[a]

Olefin	Registry no.	Cu compd	Products	Registry no.	Yield, %
1-Hexene	592-41-6	Cu_2O	2,2-Dimethylpentanoic acid	1185-39-3	45
			2-Methyl-2-ethylbutanoic acid	19889-37-3	27
			2,2-Dimethylbutanoic acid	595-37-9	3
			2,2-Dimethylpropanoic acid		1
			Higher acids		4
Cyclohexene	110-83-8	Cu_2O	1-Methylcyclopentanecarboxylic acid	5217-05-0	63
1-Heptene	592-76-7	Cu_2O	2,2-Dimethylhexanoic acid	813-72-9	57
			2-Methyl-2-ethylpentanoic acid	5343-52-2	25
1-Octene	111-66-0	Cu_2O	2,2-Dimethylheptanoic acid	14250-73-8	54
			2-Methyl-2-ethylhexanoic acid	1185-29-1	27
			2-Methyl-2-propylpentanoic acid	31113-56-1	13
1-Octene		$CuSO_4$ + Cu powder	2,2-Dimethylheptanoic acid		48
			2-Methyl-2-ethylhexanoic acid		25
			2-Methyl-2-propylpentanoic acid		10
1-Octene		Cu powder[b]	2,2-Dimethylheptanoic acid		45
			2-Methyl-2-ethylhexanoic acid		23
			2-Methyl-2-propylpentanoic acid		8
2-Octene	111-67-1	Cu_2O	2,2-Dimethylheptanoic acid		36
			2-Methyl-2-ethylhexanoic acid		30
			2-Methyl-2-propylpentanoic acid		15
1-Decene	872-05-9	Cu_2O	2,2-Dimethylnonanoic acid	14250-75-0	49
			2-Methyl-2-ethyloctanoic acid	31199-56-1	24
			2-Methyl-2-propylheptanoic acid	39037-67-7	18
			2-Methyl-2-butylhexanoic acid		6
1,5-Hexadiene[c]	592-42-7	Cu_2O	α-Ethyl-γ-valerolactone	19639-00-0	30
1,5-Cyclooctadiene[c]	111-78-4	Cu_2O	Bicyclo[3.3.0]octanecarboxylic acid	32789-48-3	15

[a] In most cases 0.2 mol of olefin, 0.02 mol of Cu compound, and 105 ml of 98% H_2SO_4 were used, the reaction temperature was approximately 30°, and the reaction time varied from 1 to 2 hr. The pressure of carbon monoxide was 1 atm. [b] The amount of Cu powder was 0.04 mol. [c] The temperature was 5–10°.

However, the equimolar mixture of a Cu(II) compound and copper powder in concentrated H_2SO_4 showed similar catalytic activity to that of Cu(I) compounds in H_2SO_4.

$$Cu^{2+} + Cu^0 \xrightarrow{\text{concd } H_2SO_4} 2Cu^+$$

Copper powder in concentrated H_2SO_4 also exhibits catalytic activity; probably it is due to the formation of Cu_2SO_4 by the oxidation with concentrated H_2SO_4. The presence of Cl^-, Br^-, I^-, NO_3^-, and CN^- inhibits the catalytic activity. These ions prevent the formation of Cu(I) tricarbonyl. The optimum reaction temperature was 20–50° for monoolefins, and 5–10° for dienes. Above 55°, side reactions such as polymerization predominate. The olefin was slowly added into the Cu(I) carbonyl suspension. When the rate of the addition of olefin was too fast, polymerization occurred in competition with the carbonylation reaction.

The influence of the concentration of H_2SO_4 was examined. The results were shown in Figure 2. At H_2SO_4 concentrations above 80%, the rate of reaction increased. No carbonylation occurred at an H_2SO_4 concentration less than 80%. The effect of the H_2SO_4 concentration upon the carbonylation is parallel to its effect upon the formation of unstable Cu(I) tricarbonyl ion $Cu(CO)_3^+$ in H_2SO_4 solution.[6] Cu(I) monocarbonyl ion $Cu(CO)^+$ is formed at H_2SO_4 concentrations less than 80%, whereas Cu(I) tricarbonyl ion, which acts as the carbonylation catalyst, is formed at H_2SO_4 concentrations above 80%. These carbonyl ions exist as an equilibrium mixture.[8]

$$Cu^+ \xrightarrow{CO} Cu(CO)^+ \xrightarrow[\text{concd } H_2SO_4]{CO} Cu(CO)_3^+$$

$$Cu(CO)_3^+ \rightleftharpoons Cu(CO)^+ + 2CO$$

$Cu(CO)_3^+$ is very unstable and easily releases CO. In the presence of CO acceptors such as carbonium ions, carbon monoxide is liberated from Cu(I) tricarbonyl ion and transferred to the CO acceptor immediately. Carbon monoxide is continuously absorbed by Cu^+ in the solution from the gas phase and kept at high concentrations as a form of $Cu(CO)^+$ or $Cu(CO)_3^+$. In the reaction system Cu^+ acts as "CO carrier" from the gas phase to reaction species in the solution.

The structures of the products were convincingly determined by nmr, ir, and mass spectra as well as elemental analysis. In most cases the products were

(8) The CO absorptions by Cu_2O were studied in various H_2SO_4 concentrations. At the H_2SO_4 concentrations less than 80%, the mole ratio of CO/Cu^+ was 1.0. However, CO/Cu^+ gradually increased with the increase of H_2SO_4 concentrations. CO/Cu^+ was 1.05 (85%), 1.20 (90%), 1.33 (95%), 1.50 (100%) at 20°. Moreover, at elevated CO pressures until 18 atm, the absorption of CO by Cu_2O was studied in concentrated H_2SO_4. The mole ratio of CO/Cu^+ reached 3 at −10° (CO 7 atm). CO/Cu^+ are shown as follows, in 100% H_2SO_4.

CO, atm	−10°	0°	20°
1	2.2	1.8	1.5
7	3.0	2.8	2.2
10	3.0	3.0	2.3
18	3.0	3.0	2.6

Thus the equilibrium of $Cu(CO)^+$ and $Cu(CO)_3^+$ was concluded (see ref 6).

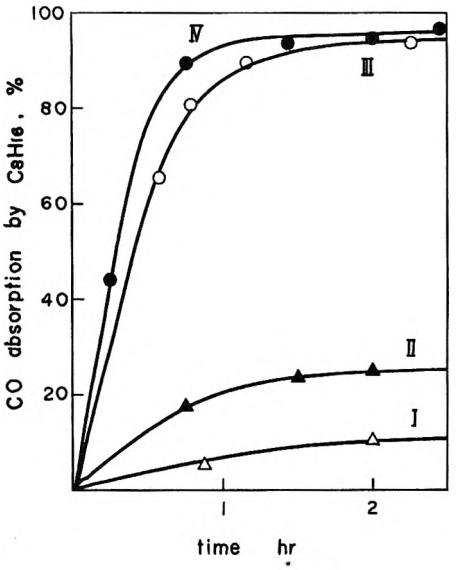


Figure 1.—Catalytic effect of Cu(I) compound. Cuprous oxide was used as Cu(I) compound [98% H_2SO_4 (2 mol) and 1-octene (0.2 mol) at 35°]: I ,Cu_2O (0 mmol); II, Cu_2O (1 mmol); III, Cu_2O (20 mmol); IV, Cu_2O (40 mmol).

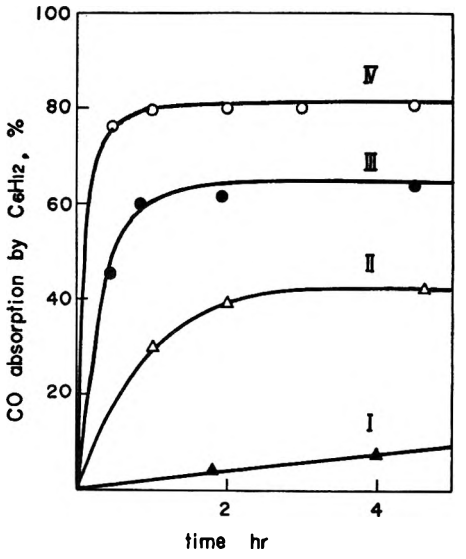
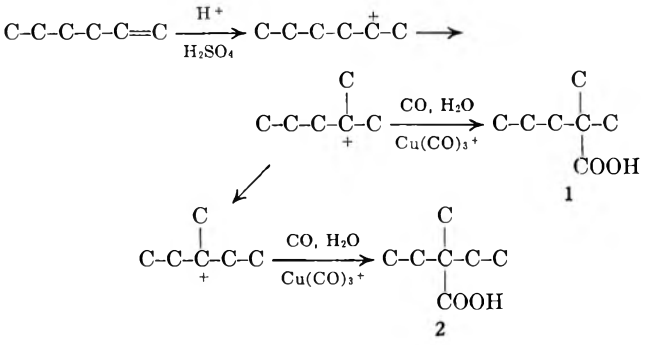


Figure 2.—The influence of H_2SO_4 concentration, with Cu_2O (20 mmol) and 1-hexene (200 mmol) at 30°: I, 85% H_2SO_4; II, 88% H_2SO_4; III, 92% H_2SO_4; IV, 98% H_2SO_4.

mixtures of the isomers. When the mixtures of the isomers were separable by glpc, each isomer was isolated by preparative glpc and was subjected to structure analysis. When the separation of isomers was not easily performed by glpc, the mixture was analyzed by ^{13}C nmr.

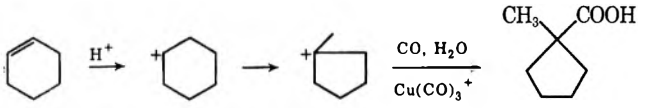
1-Hexene reacts with carbon monoxide. 2,2-Dimethylpentanoic acid (1) and 2-methyl-2-ethylbutanoic acid (2) were obtained and separated by glpc. First,



1-hexene is protonated and the resulting carbonium ion rearranges to the *tert*-carbonium ion. The skeleton rearrangement take place subsequently, then the *tert*-carbonium ion reacts with carbon monoxide. Other acyclic olefins react with carbon monoxide similarly. 1-Heptene gives 2,2-dimethylhexanoic acid and 2-methyl-2-ethylpentanoic acid.

The products, obtained from 1-octene, 2-octene, and 1-decene, were not separated by glpc, but the structure and the ratio of each isomer of the mixture were convincingly determined by ^{13}C nmr. 1-Octene and 2-octene give 2,2-dimethylheptanoic acid, 2-methyl-2-ethylhexanoic acid, and 2-methyl-2-propylpentanoic acid. 1-Decene gives 2,2-dimethylnonanoic acid, 2-methyl-2-ethyloctanoic acid, 2-methyl-2-propylheptanoic acid, and 2-methyl-2-buthylhexanoic acid. Finally, the structures of all the products were determined by ^{13}C nmr. ^{13}C chemical shift assignments of each compound are shown in Chart I.

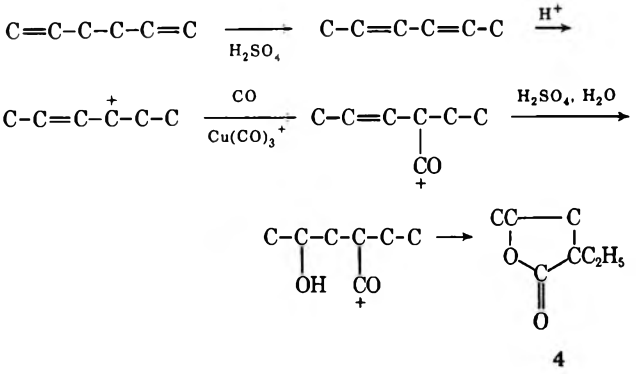
In cyclohexene carbonylation proceeds after the rearrangement to methylcyclopentane carbonium ion. Compound **3** was shown to be 1-methylcyclopentane-



carboxylic acid by its characteristic ^1H nmr methyl signal at δ 1.28 (s).

1,5-Hexadiene gives the γ-valerolactone derivative. The reaction scheme is not simple. The first step of the reaction is the protonation of one of the double bonds, which is followed by rearrangement and CO addition. Presumably another double bond is successively hydroxylated and the OH group is esterified intramolecularly. This is the only exception to the formation of *tert*-carboxylic acids from olefins tested in our experiments.

Compound **4** was determined to be α-ethyl-γ-valerolactone from its characteristic ^1H nmr signals at δ 1.40

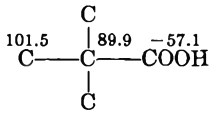


(d, CH_3CHO–), 1.00 (t, CH_3CH_2–), 2.05 (m, –CO-CHC_2H_5), and 4.50 (m, CH_3CHO–). Mass spectra showed *m/e* (rel intensity) 128 (10, M^+), 113 (12), 100 (62), 55 (100).

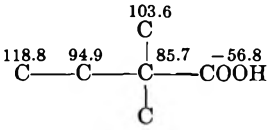
1,5-Cyclooctadiene gives bicyclo[3.3.0]octanecarboxylic acid. The scheme involving the transannular

CHART I.—^{13}C CHEMICAL SHIFTS OF *tert*-CARBOXYLIC ACIDS[a]

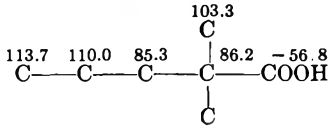
tert-C_5 acid

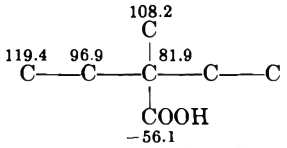


tert-C_6 acid

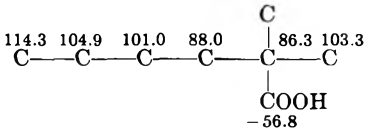


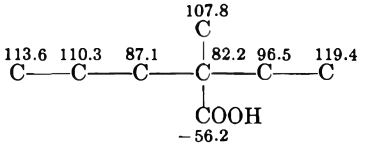
tert-C_7 acid



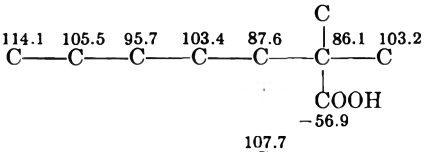


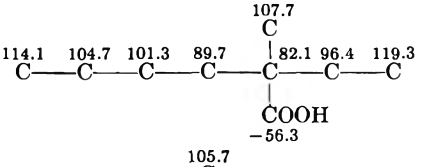
tert-C_8 acid

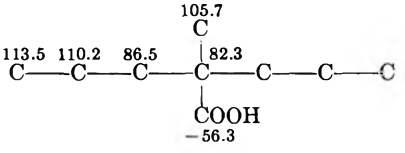




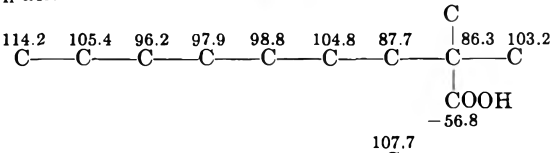
tert-C_9 acid

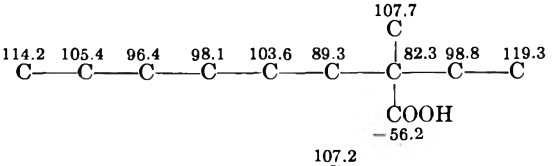


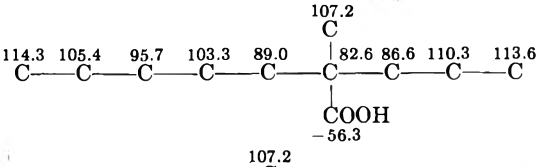


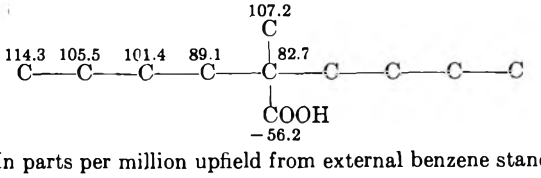


tert-C_{11} acid



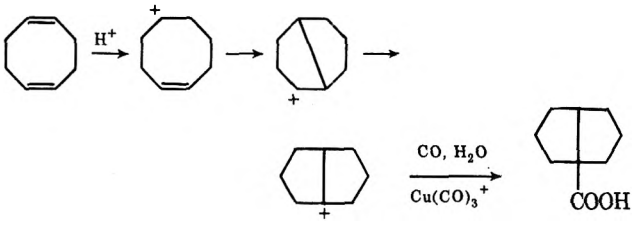






[a] In parts per million upfield from external benzene standard.

addition of the carbonium ion to the second double bond may be taken to explain the product. The typical ^{1}H nmr spectra of **5** appear at δ 2.70 (m, -CH-).



5

Mass spectra showed *m/e* (rel intensity) 154 (32, M^+), 113 (93), 109 (75), 67 (100).

Experimental Section

The infrared spectra were taken on neat samples on a Hitachi EPI-S2. ^{1}H nmr spectra were taken on a JEOL PS-100 at 100 MHz in CCl_4 solvent. Chemical shifts are given in δ units (parts per million) downfield from internal tetramethylsilane. Completely proton-decoupled ^{13}C nmr spectra were obtained at 15.1 MHz on a JEOL PS-100 spectrometer equipped with the SD-HC heterospin decoupler and IS-100 field-frequency synchronous sweep system of the proton-irradiating frequency. Complete analysis and discussion of ^{13}C nmr were given elsewhere.[9] Mass spectra were measured on the Shimazu LKB-9000 gas chromatograph–mass spectrometer with 70 eV ionizing current. Glpc analysis was performed using a 3M FFAP column (10% on Chromosorb WAW). Elemental analyses were done on a Yanagimoto CHN MT-2.

Reagents.—1-Hexene, 1-heptene, 1-octene, 2-octene, 1-decene, cyclohexene, 1,5-hexadiene, and 1,5-cyclooctadiene were all commercial reagents and were purified by distillation.

Cu_2O, $CuSO_4$, Cu powder, carbon monoxide, and 98% H_2SO_4 were all commercial reagents, which were used without further purification.

Preparation of Cu(I) Carbonyl.—In a 1-l. three-necked flask equipped with a thermometer and a carbon monoxide gas buret were placed 2.86 g (0.02 mol) of Cu_2O and 105 ml (2 mol) of 98% H_2SO_4. The apparatus was evacuated by a diffusion pump to remove air, and then carbon monoxide was introduced from the gas buret. The mixture of Cu_2O and H_2SO_4 was stirred vigorously. Carbon monoxide was absorbed by cuprous ion in about 40 min. The ratio of CO/Cu^+ reached 1.35 at 30° (CO 1 atm).

Carbonylation of Olefin.—From a syringe, 24.8 ml (0.2 mol) of 1-hexene was added dropwise during 50 min to the Cu(I) carbonyl suspension. Carbon monoxide was soon absorbed and treated with olefin. CO absorption was finished in 1–2 hr, and the reaction mixture was poured over ice–water. The products were extracted by benzene. Excess alkali was added to the benzene extract. The water phase was acidified by H_2SO_4. Carboxylic acids were again extracted by benzene. The products of 1 and 2 were isolated by preparative glpc. The structures of products were determined by ir, nmr, and mass spectra as well as elemental analysis.

2,2-Dimethylbutanoic acid was obtained by the carbonylation of 1-hexene as a by-product: bp 163°; n^{25}D 1.4205 [lit.[10] bp 96° (20 mm), n^{20}D 1.4142]; d^{25}_4 0.9293; ir 2990, 1705 (C=O), 1260 1190 cm^{-1}; nmr δ 0.90 (t, 3, J = 7 Hz, $-CH_2CH_3$), 1.20 (s, 6, CH_3CCOOH), 1.62 (q, 2, J = 7 Hz, $-CH_2CH_3$), 10.9 (s, 1, COOH).

Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 61.75; H, 10.31.

***tert*-C_7 carboxylic acids** were obtained by the carbonylation of 1-hexene. The products were the mixtures of 2,2-dimethylpentanoic acid (1) and 2-methyl-2-ethylbutanoic acid (2): bp 194°; n^{25}D 1.4248 [lit.[10] bp 110–114° (20 mm), n^{20}D 1.4208–1.4242]; d^{25}_4 0.9207; ir of separated 1 2980, 1710 (C=O), 1480, 1240, 1190 cm^{-1}; ir of separated 2 2990, 1708 (C=O), 1470, 1260, 1185 cm^{-1}; ^{1}H nmr of separated 1 δ 0.92 (t, 3, J = 7 Hz, CH_3CH_2–), 1.18 (s, 6, CH_3C–), 1.49 (m, 4, $-CH_2$–), 11.03 (br s,

(9) J. Iyoda, Y. Souma, and H. Sano, *Bull. Gov. Ind. Res. Inst., Osaka*, **23**, 197 (1972).

(10) H. Koch and W. Haff, *Justus Liebigs Ann. Chem.*, **618**, 251 (1958).

1, COOH); ^{1}H nmr of separated 2 δ 0.90 (t, 6, J = 7 Hz, CH_3-CH_2–), 1.12 (s, 3, CH_3C–), 1.55 (m, 4, CH_3CH_2–), 10.9 (br, s, 1, COOH).

Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.34; H, 11.05.

***tert*-C_8 carboxylic acids** were obtained by the carbonylation of 1-heptene. The products were the mixtures of 2,2-dimethylhexanoic acid (A) and 2-methyl-2-ethylpentanoic acid (B): bp 214°; n^{25}D 1.4310; d^{25}_4 0.9154; ir 2950, 1700 (C=O), 1470, 1280, 1180 cm^{-1}; ^{1}H nmr of separated A δ 0.95 (t, 3, J = 6 Hz, CH_3CH_2–), 1.20 (s, 6, CH_3C–), 1.36 (m, 6, –CH_2–), 11.5 (br, s, 1, COOH); ^{1}H nmr of separated B δ 0.92 (t, 6, J = 7 Hz, CH_3CH_2–), 1.13 (s, 3, CH_3C–), 1.44 (m, 6, –CH_2–), 11.40 (br s, 1, COOH).

Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.19; H, 11.11.

***tert*-C_9 carboxylic acids** were obtained by the carbonylation of 1-octene and 2-octene. The products were the mixtures of 2,2-dimethylheptanoic acid, 2-methyl-2-ethylhexanoic acid, and 2-methyl-2-propylpentanoic acid with the ratio of 4:2:1: bp 132–133° (15 mm); n^{25}D 1.4291; d^{25}_4 0.9037; ir 2950, 1705 (C=O), 1470, 1205 cm^{-1}; ^{1}H nmr δ 1.12, 1.19 (s, CH_3CCOOH), 10.9 (br, 2, –COOH).

Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 67.93; H, 11.78.

***tert*-C_{11} carboxylic acids** were obtained by the carbonylation of 1-decene. The products were the mixtures of 2,2-dimethylnonanoic acid, 2-methyl-2-ethyloctanoic acid, 2-methyl-2-propylheptanoic acid, and 2-butylhexanoic acid with the ratio of 8:4:3:1: bp 142–143° (7 mm); n^{25}D 1.4368 [lit.[10] bp 139–148.5° (20 mm), n^{20}D 1.4363]; d^{25}_4 0.8976; ir 2950, 1700 (C=O), 1470, 1260 cm^{-1}; ^{1}H nmr δ 1.12, 1.18 (s, CH_3CCOOH), 9.80 (br, s, –COOH).

Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 71.01; H, 12.22.

1-Methylcyclopentanecarboxylic acid was obtained by the carbonylation of cyclohexene: ir 2980, 1705 (C=O), 1460, 1280, 1200 cm^{-1}; ^{1}H nmr δ 1.28 (s, 3, CH_3C–), 1.70 (m, 6, –CH_2–), 2.16 (m, 2, –HCHCCOOH), 11.78 (br, s, –COOH).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 66.02; H, 9.57.

α-Ethyl-γ-valerolactone was obtained by the carbonylation of 1,5-hexadiene: ir 2950, 1760 (C=O), 1460, 1175 cm^{-1}; ^{1}H nmr δ 1.00 (t, 3, J = 7 Hz, CH_3CH_2–), 1.40 (d, 3, J = 7 Hz, CH_3-CH–), 1.70 (m, 2, –CH_2–), 2.05 (m, 1, –CHC_2H_5), 2.50 (m, 2, –CH_2–), 4.50 (m, 1, –CHO–); mass spectrum (70 eV) m/e (rel intensity) 128 (10, M^+), 113 (12), 100 (62), 56 (90), 55 (100), 41 (88).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.15; H, 9.42.

Bicyclo[3.3.0]octanecarboxylic acid was obtained by the carbonylation of 1,5-cyclooctadiene: ^{1}H nmr δ 2.70 (m, 1, –CH–), 1.00–2.30 (m, 12, –CH_2–), 10.8 (br, s, –COOH); mass spectrum (70 eV) m/e (rel intensity) 154 (32, M^+), 126 (73), 113 (93), 109 (75), 67 (100).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.24; H, 8.76.

Registry No.—Carbon monoxide, 630-08-0; Cu_2O, 1317-39-1; H_2SO_4, 7664-93-9.

Steric Effects in the Cupric Ion Oxidation of α-Ketols[1]

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The kinetics of the oxidation of a series of α-ketols by copper(II) in buffered aqueous pyridine have been studied spectrophotometrically. At concentrations of cupric ion greater than 0.025 M the reaction exhibits first-order dependence with respect to copper(II), which is typical of a mechanism involving a rate-determining enolization of a copper(II)–ketol complex. The following order of reactivities was observed: α-hydroxyacetophenone > 2-hydroxycyclohexanone = benzoin > 4,4′-dimethoxybenzoin > 3-hydroxy-2-butanol > 2-hydroxycyclopentanone > 4-hydroxy-3-hexanone > 4-hydroxy-2,5-dimethyl-3-hexanone ≫ 4-hydroxy-2,2,5,5-tetramethyl-3-hexanone. In the cases of benzoin, 4,4′-dimethoxybenzoin, and 2-hydroxycyclopentanone large negative entropies of activation and large deviations from first-order kinetics were observed. These kinetic results are interpreted in terms of an intermediate copper(II)–ketol complex possessing a chelate structure.

Although the copper(II) oxidation of reducing sugars in alkaline aqueous media has been known for a very long time,[2] it has only been more recently that the mechanism of the reaction has been investigated.[3–7] The reaction is quite general for primary and secondary alcohols which possess an α-carbonyl group and is synthetically useful for the oxidation of acyloins to the corresponding diketones.[8] Weissberger, Schwarze, and Mainz[3] found that the oxidation of benzoin to benzil by ethanolic Fehling's solution was first order with respect to both the concentration of ketol and hydroxide ion, but was zero order with respect to copper(II) as shown by eq 1. In addition, it was found that the rates of

$$C_6H_5C(=O)CH(OH)C_6H_5 + 2OH^- + 2Cu^{2+} \longrightarrow C_6H_5C(=O)C(=O)C_6H_5 + 2H_2O + 2Cu^+$$

$$-\frac{d[Cu(II)]}{dt} = k[C_6H_5C(=O)CH(OH)C_6H_5][OH^-] \quad (1)$$

autoxidation and racemization of benzoin, under identical conditions, obeyed the same rate law and proceeded at the same rate as the copper(II) oxidation.[9] Kinetic behavior of this type is indicative of an initial rate-determining enolization. Marshall and Waters[6] observed a similar behavior when they investigated the oxidation of acetoin and benzoin with Benedict's solution.

(1) This work was supported by grants from the Research Corporation and the University of Puget Sound Research Council.

(2) Trommer, *Ann. Chem. Pharm.*, **39**, 360 (1841); *Chem. Zentr.*, **12**, 762 (1841).

(3) A. Weissberger, W. Schwarze, and H. Mainz, *Justus Liebigs Ann. Chem.*, **481**, 68 (1930).

(4) J. Parrod, *C. R. Acad. Sci.*, **212**, 610 (1941).

(5) M. P. Singh, *et al.*, *Z. Phys. Chem. (Leipzig)*, **204**, 1 (1955); **205**, 285, 294 (1956); **207**, 187, 198 (1957); **208**, 265, 273 (1958); **216**, 13 (1961); **240**, 400 (1969); *J. Amer. Chem. Soc.*, **92**, 537 (1970).

(6) B. A. Marshall and W. A. Waters, *J. Chem. Soc.*, 2392 (1960); 1579 (1961).

(7) K. B. Wiberg and W. G. Nigh, *J. Amer. Chem. Soc.*, **87**, 3849 (1965).

(8) W. G. Nigh in "Oxidation in Organic Chemistry," part B, W. S. Trahanovsky, Ed., Academic Press, New York, N. Y., 1973, Chapter 1.

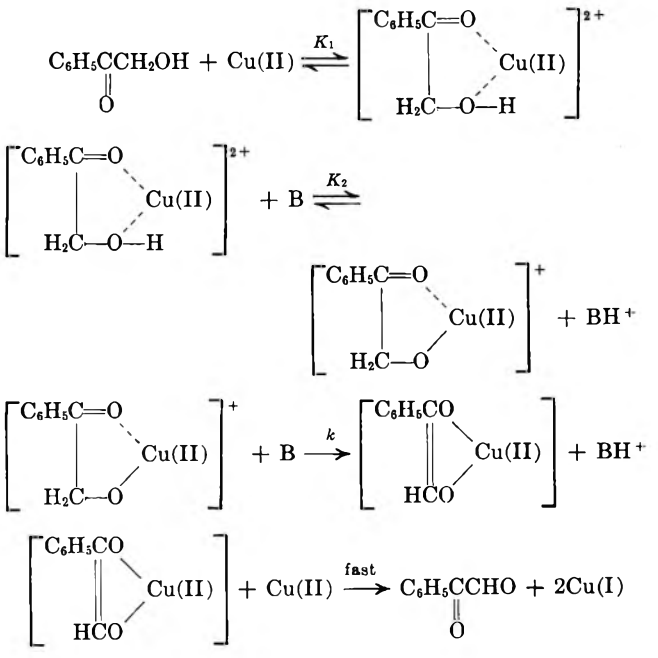
(9) A. Weissberger, H. Mainz and E. Strasser, *Chem. Ber.*, **62**, 1942 (1929); A. Weissberger, A. Dorken, and E. Strasser, *ibid.*, **64**, 1200 (1931).

Somewhat different results were obtained by Wiberg and Nigh[7] when they investigated the oxidation of α-hydroxyacetophenone with cupric acetate in buffered aqueous pyridine. This reaction was found to obey the rate law of eq 2, where the second term exhibits a β-order dependence on base.

$$-\frac{d[Cu(II)]}{dt} = k_1[C_6H_5CCH_2OH][B] + k_2[C_6H_5CCH_2OH][B][Cu(II)] \quad (2)$$

Since the basicity of the reaction media may be held essentially constant, it was possible to demonstrate a base catalysis (*i.e.*, $\beta > 0$). However, a quantitative evaluation of β was prohibited by the complexity of the media. Thus the media contain four different bases (*i.e.*, OH^-, $CH_3CO_2^-$, C_5H_5N, and H_2O) each of which might catalyze the reaction. In addition, pyridine and acetate ion are potential complexing agents for cupric ion.

At low concentrations of cupric ion (*i.e.*, $k_1 \gg k_2$[Cu(II)]) the first term in eq 2 predominates and becomes identical with the rate of deuterium exchange (*i.e.*, enolization) under the same reaction conditions. Thus, under these conditions, eq 2 becomes identical with eq 1 and represents the same reaction pathway which operates in aqueous media. At higher concentrations of cupric ion (*i.e.*, k_2[Cu(II)] $\gg k_1$) the second term in eq 2 predominates and was found to exhibit a kinetic isotope effect of 7.4 (25°) and a Hammett reaction constant, ρ, of +1.24. This is strong evidence for a second reaction pathway involving a rate-determining proton removal from the α-methylene position of a copper(II)–ketol complex. The following mechanism[8] has been proposed for this copper(II)-catalyzed reaction.



This paper offers additional experimental data which further support the chelate structure of the copper(II)–ketol intermediate proposed in the above mechanism.

Results

The copper(II) oxidation of a series of α-ketols was investigated in buffered (0.10 *M* pyridinium acetate) 50 mol % aqueous pyridine. Oxygen was excluded during the reaction by degassing the reactants prior to sealing the reaction cells under vacuum or under an atmosphere of purified nitrogen. Under these conditions, tetrapyridinecopper(I) is stable in solution, allowing the reaction to be studied under homogeneous conditions.

The rate of disappearance of copper(II) was followed spectrophotometrically (800–900 nm) under pseudo-first-order conditions. The initial concentration of cupric acetate was always in excess of 0.025 *M* in order to ensure that only the copper(II)-catalyzed mechanism was kinetically observable. All of the kinetic results reported in this paper pertain only to the second term of the rate law (eq 2). Even under these reaction conditions benzoin, 4,4′-dimethoxybenzoin, and 2-hydroxycyclopentanone exhibited deviations from first-order behavior during the second half-life. The other ketols gave linear plots of ln $(A_t - A_\infty)$ *vs.* time well beyond 75% reaction. The slope of these plots yields the pseudo-first-order rate constant, k_{obsd}. The apparent second-order rate constant, k_2, is obtained by dividing k_{obsd} by the corresponding initial concentration of the ketol. The raw kinetic data were also computer analyzed by a least squares program.[10] These refined data are presented in Table I. The reported second-order rate constants (through the second half-life, except where indicated) are numerical averages of from two to five separate kinetic runs and the uncertainties are average deviations.

TABLE I
RATES OF REDUCTION OF COPPER(II) BY α-KETOLS IN 50 MOL % PYRIDINE–WATER

Ketol	[Cu(II)]	[Ketol]	Temp, °C	10^3k_2, l. mol^{-1} min^{-1}
3-Hydroxy-2-butanone	0.100	1.00	30.1	2.70 ± 0.03
	0.025	1.00	31.1	2.83 ± 0.01
	0.025	1.00	39.4	6.35 ± 0.02
	0.025	1.00	40.3	6.62 ± 0.02
	0.025	0.50	40.3	6.92 ± 0.08
	0.025	1.00	48.6	17.4 ± 0.3
	0.025	1.00	50.0	19.1 ± 0.5
	0.025	1.00	50.3	18.2 ± 0.3
4-Hydroxy-3-hexanone	0.100	1.00	30.0	1.53 ± 0.01
	0.100	1.00	40.0	4.63 ± 0.10
	0.100	1.00	50.0	12.3 ± 0.1
4-Hydroxy-2,5-dimethyl-3-hexanone	0.100	1.00	30.0	1.21 ± 0.01
	0.100	1.00	40.0	3.43 ± 0.04
	0.100	1.00	50.0	10.0 ± 0.3
4-Hydroxy-2,2,5,5-tetramethyl-3-hexanone	0.100	1.00	50.0	$<10^{-2}$
2-Hydroxycyclopentanone	0.025	1.00	35.0	4.40 ± 0.02[a]
	0.025	1.00	45.0	8.71 ± 0.17[a]
	0.025	1.00	55.0	23.3 ± 1.0[a]
2-Hydroxycyclohexanone	0.025	0.50	20.0	7.96 ± 0.09
	0.025	0.50	30.1	26.6 ± 0.2
	0.025	0.50	41.0	86.3 ± 1.3
Benzoin	0.025	0.30	25.4	22.7 ± 0.2[a]
	0.025	0.30	34.35	42.4 ± 3.3[a]
	0.025	0.30	44.0	124 ± 17[a]
4,4′-Dimethoxybenzoin	0.025	0.40	24.9	6.43 ± 0.40[a]
	0.025	0.40	35.0	18.7 ± 0.70[a]
	0.025	0.40	45.2	45.8 ± 0.25[a]

[a] Rate constants calculated for the first half-life.

(10) K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, p 554.

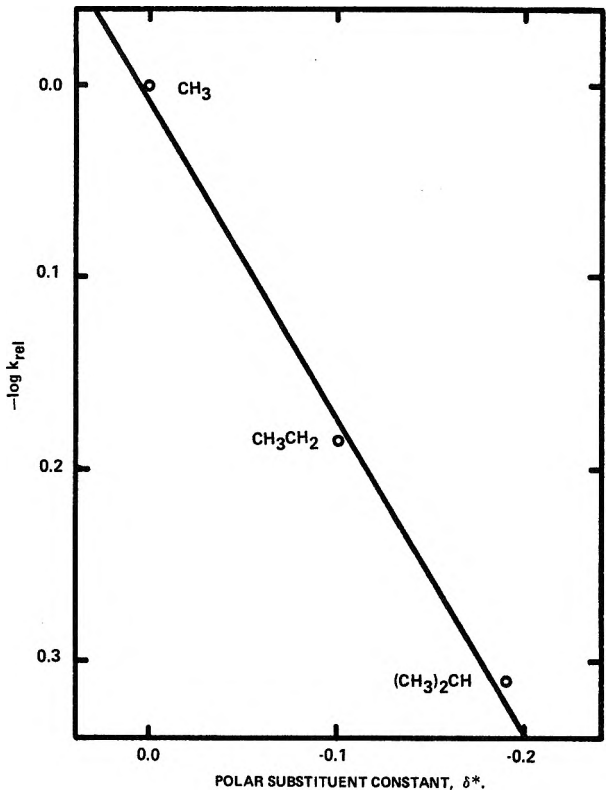


Figure 1.—Linear free energy plot for the oxidation of α-ketols by copper(II).

The relative rates of oxidation and the activation parameters are presented in Table II. The enthalpies

TABLE II

SUMMARY OF KINETIC PARAMETERS FOR THE COPPER(II)-CATALYZED OXIDATION OF α-KETOLS IN 50 MOL % PYRIDINE-WATER

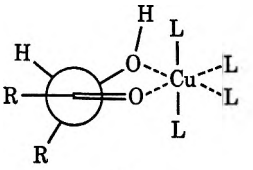
Ketol	k_{rel} (40°)	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
3-Hydroxy-2-butanone	1.0	18.6 ± 0.6	−18
4-Hydroxy-3-hexanone	0.65	19.4 ± 0.6	−16
4-Hydroxy-2,5-dimethyl-3-hexanone	0.49	19.6 ± 0.6	−15
4-Hydroxy-2,2,5,5-tetramethyl-3-hexanone	$<10^{-3}$		
2-Hydroxycyclopentanone	0.86	14 ± 1.5	−31
2-Hydroxycyclohexanone	11	19.2 ± 0.4	−11
Benzoin	11	15 ± 1.5	−24
4,4′-Dimethoxybenzoin	4.0	17.4 ± 0.6	−18
α-Hydroxyacetophenone[a]	49[b]	18.9 ± 0.4	−9

[a] From ref 7. [b] Corrected for statistical factor.

of activation were calculated from the slope of plots of log (k/T) *vs.* $1/T$ and the relative rates and entropies of activation were calculated at 40°.

Discussion

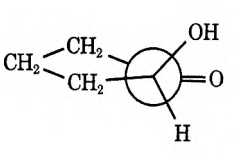
The most dramatic rate effect in Table II involves 4-hydroxy-2,2,5,5-tetramethyl-3-hexanone (pivaloin). This ketol does not exhibit any detectable oxidation by cupric ion even after 1 week at 50°. Under identical conditions, the oxidation of 4-hydroxy-2,5-dimethyl-3-hexanone (isobutyroin) was 50% complete after about 1 hr. The 1,2-nonbonding interactions associated with two skewed *tert*-butyl groups completely excludes any possibility of a planar chelate structure such as I.



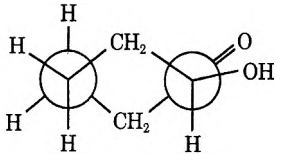
I

The tremendous steric strain involved in such a chelate is best demonstrated with space-filled molecular models. When R is isopropyl the methyl groups can rotate to the outside (*i.e.*, away from one another), thereby reducing the steric hindrance. This mechanism for the relief of steric strain is also supported by the similarity of the activation parameters for 3-hydroxy-2-butanone (acetoin, R = methyl), 4-hydroxy-3-hexanone (propionoin, R = ethyl), and isobutyroin (R = isopropyl). The observed rate differences for these three ketols are consistent with the value of +1.24 previously reported for the Hammett reaction constant, ρ.[7] This is demonstrated by the linearity (within experimental error) of a plot (Figure 1) of log k_{rel} *vs.* the polar substituent constant, σ^*. A value of +1.3 for the polar reaction constant, ρ^*, was obtained from the slope of Figure 1. A similar sensitivity to electronic effects is observed in the case of benzoin and 4,4′-dimethoxybenzoin. The electron-releasing effect of the methoxy groups decreases the rate of reaction.

The sensitivity of the reaction to steric effects is also encountered in the case of the alicyclic α-ketols, 2-hydroxycyclopentanone (II) and 2-hydroxycyclo-



II



III

hexanone (III). In structure II the carbonyl oxygen must be skewed between the hydroxy group and the enolizable hydrogen, whereas in structure III the carbonyl group is eclipsed by the hydroxy group. Therefore the internuclear oxygen–oxygen distance must be greater in II than in III. Crude measurements of molecular models indicate that this distance is approximately 30% greater in II. Thus, II cannot readily achieve the nearly planar conformation which is required for the maximum stability of the chelate, I. In contrast, III is perfectly aligned for the formation of the chelate ring. This large difference in the stability of the alicyclic chelates is reflected in the very large negative entropy of activation exhibited by II and the relatively small negative value obtained for III. In addition to this entropy effect, III is oxidized 13 times faster than II under identical reaction conditions. This difference in the rate of reaction cannot be due to some inherent ability of III to enolize, since cyclopentanone undergoes base-catalyzed enolization about seven times faster than cyclohexanone.[11] The more facile enolization of the five-membered ring is further demonstrated by the lower enthalpy of activation exhibited by II.

(11) H. Shechter, M. J. Collis, R. Dessy, Y. Okuzumi, and A. Chen, *J. Amer. Chem. Soc.*, **84**, 2905 (1962).

A comparison of the entropies of activation for benzoin and α-hydroxyacetophenone further supports the chelate structure of the reaction intermediate. The presence of a single aryl group in structure I does not produce any appreciable steric interaction. If a second aryl group is present, however, considerable steric strain is introduced, resulting in the larger negative entropy of activation for benzoin.

Although the application of eq 2 for all of the α-ketols investigated has not been rigorously demonstrated, such an assumption seems justified by the general kinetic results obtained. In addition, the kinetic data have been interpreted in terms of steric hindrance to the formation of an intermediate chelate, but there should also be a corresponding effect on the enolization step. Thus, as the steric bulk around the enolizable proton increases, the ability of a base to attack the proton must decrease (*i.e.*, the rate of enolization decreases). In summary, therefore, a mechanism for the copper(II)-catalyzed oxidation of α-ketol in aqueous pyridine which involves an initial rate-determining proton removal from the α position of a copper(II)–ketol chelate is compatible with all of the available experimental evidence.

Experimental Section

Reagents.—Cupric acetate monohydrate (J. T. Baker, reagent grade), pyridine (Aldrich, reagent grade), and acetic acid (Du Pont, reagent grade) were used as obtained from commercial sources. Benzoin and 4,4′-dimethoxybenzoin (Matheson Coleman and Bell) were recrystallized several times from ethanol. The 3-hydroxy-2-butanone (Aldrich) was purified by the method of Marshall and Waters,[6] while 4-hydroxy-3-hexanone, 4-hydroxy-2,5-dimethyl-3-hexanone, and 4-hydroxy-2,2,5,5-tetramethyl-3-hexanone were prepared and purified by the method of Snell and McElvain.[12] The 2-hydroxycyclohexanone and 2-hydroxycyclopentanone were prepared and purified by the method of Schrapler and Ruhlmann.[13] In these last two reactions, the ester was slowly added through a Soxhlet extractor instead of the usual diluting head.

Kinetic Method.—Solutions of cupric acetate and the α-ketol were prepared in 50 mol % aqueous pyridine containing acetic acid to buffer the solutions. In the case of the less reactive systems, equal amounts of each solution were placed in a special Pyrex reaction cell which had previously been cooled to Dry Ice–acetone temperature. The reaction mixture was carefully degassed on a vacuum line by successive freezing and melting. The cell was sealed under vacuum (or under an atmosphere of purified nitrogen) and stored at the Dry Ice temperature until ready for use. The run was initiated by quickly bringing the reaction cell to the desired reaction temperature in a constant-temperature bath. At appropriate time intervals the cells were removed from the bath and placed in a thermostated cell compartment of a Beckman DU spectrophotometer. After the absorption of the reaction mixture was measured, the cell was returned to the bath. In the case of the more reactive reaction systems, the copper(II) solution was isolated from the ketol solution during the degassing using reaction cells similar to those described by Wiberg and Lepse.[14]

Registry No.—Copper, 7440-50-8.

(12) J. M. Snell and S. M. McElvain, "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 114.
(13) U. Schrapler and K. Ruhlmann, *Chem. Ber.*, **97**, 1383 (1964).
(14) K. B. Wiberg and P. A. Lepse, *J. Amer. Chem. Soc.*, **86**, 2612 (1964)

Reactions of Polyarylated Carbinols. III.[1] Base-Catalyzed Rearrangement of 1,2,3,4,5-Pentaphenyl-2,4-cyclopentadien-1-ol[2]

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The base-catalyzed rearrangement of 1,2,3,4,5-pentaphenyl-2,4-cyclopentadien-1-ol (1) to 2,3,4,5,5-pentaphenyl-2-cyclopenten-1-one (4) has been observed and its mechanism has been investigated. This rearrangement has been found to occur with a wide variety of bases [sodium hydroxide, sodium carbonate, sodium bicarbonate, sodium amide, hexamethylphosphoramide (HMPA), and *N,N*-diethylformamide (*N,N*-DEF)], at various temperatures (173 and 95°), and after various reaction periods (3 and 8 hr). Mechanistic investigations established that the completely delocalized carbanion **7** is formed during the reaction and that 2,2,3,4,5-pentaphenyl-3-cyclopenten-1-one (**3**) is an intermediate in this rearrangement. It was further established that ketone **3** is the kinetically controlled product of this rearrangement while ketone **4** is the thermodynamically controlled product.

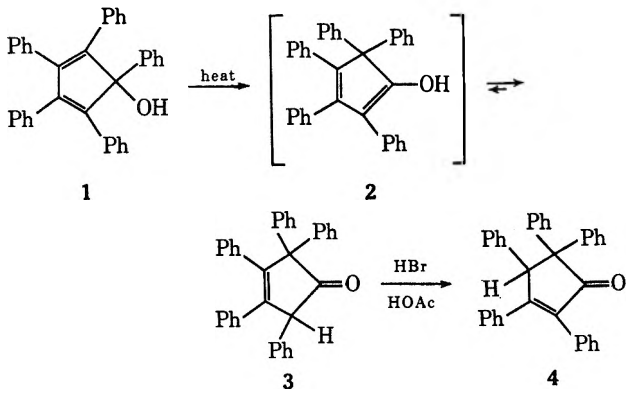
We have previously reported[1a] that 2,3,4,5,5-pentaphenyl-2-cyclopenten-1-one (**4**) could be prepared from 1,2,3,4,5-pentaphenyl-2,4-cyclopentadien-1-ol (**1**) *via* the following sequence of reactions: a thermally induced [1,5] sigmatropic phenyl rearrangement to give 2,2,3,4,5-pentaphenyl-3-cyclopenten-1-one (**3**), *via* the keto–enol tautomerization of the dienol intermediate **2**, followed by treatment of the ketone **3** with acid (HBr/HOAc) (Scheme I).

We now wish to report the direct base-catalyzed rearrangement of the dienol **1** to the ketone **4**. In addition to the interesting mechanistic aspects of this rearrangement, it also affords a simpler one-step preparative procedure for ketone **4** in greater yields than the preparative sequence represented in Scheme I.

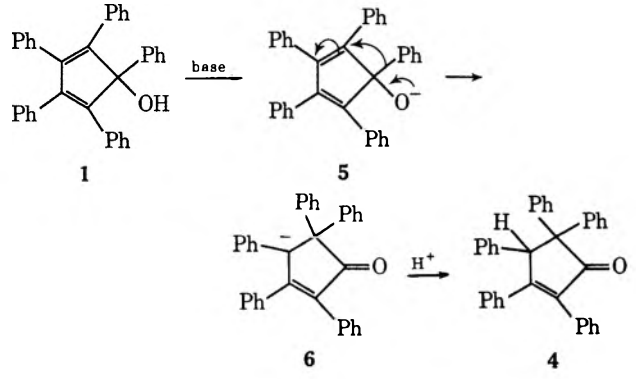
Initial treatment of dienol **1** with base followed by aqueous quench and work-up afforded only one product, ketone **4**. Based upon these results the initial mechanism postulated for this rearrangement involved formation of the alcoholate **5**, followed by phenyl migration to produce the enolate **6**, which was then protonated upon aqueous quenching to give the final product, ketone **4** (Scheme II). However, one objection to the above mechanism which arises is that ketone **4** is the only product obtained from this reaction. This objection arises because if the anion **6** is indeed formed it should not exist as a localized carbanion but as a com-

(1) For previous papers in this series see (a) A. K. Youssef and M. A. Ogliaruso, *J. Org. Chem.*, **37**, 2601 (1972); (b) *ibid.*, **38**, 487 (1973).
(2) Presented at the 24th Southeastern Regional Meeting of the American Chemical Society, Birmingham, Ala., Nov 3, 1972.
(3) Taken from the Ph.D. Thesis of A. K. Y. submitted to the faculty of the Department of Chemistry, VPI and SU, in partial fulfillment of the requirements for the Ph.D., July 8, 1972.

SCHEME I

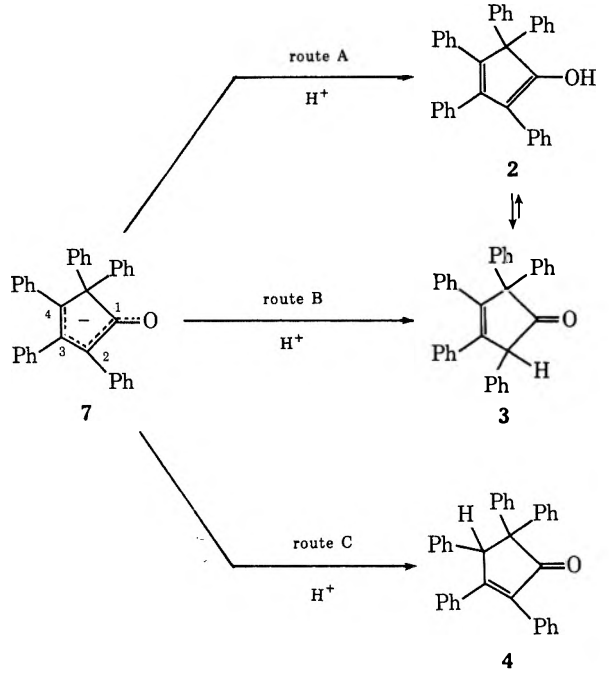


SCHEME II



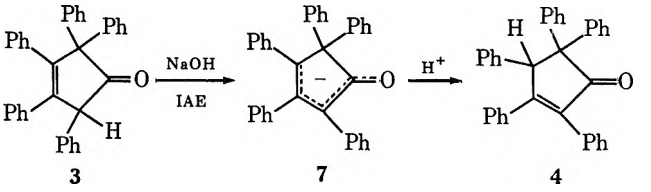
pletely delocalized carbanion, delocalized with the carbon–carbon double bond and the carbonyl group with which it is conjugated. Thus, as shown in Scheme IV, at least three resonance forms can be drawn for anion **6**, which are all best represented by the completely delocalized structure **7**. Subsequent protonation of anion **7** should then produce more than one product, since protonation could take place at three possible sites as shown below in Scheme III: at the

SCHEME III



oxygen atom (route A), at carbon 2 (route B), and at carbon 4 (route C).

Inspection of Scheme III shows that of the three possible products formed from the quench of anion **7**



only two products, ketone **3** and ketone **4**, should actually be obtained, since the enol **2** has previously[1a] been observed to tautomerize to ketone **3**. Since the only product obtained from the base-catalyzed rearrangement of dienol **1** is ketone **4**, we were led to the conclusion that possibly ketone **3** was an intermediate in this rearrangement, and that under the conditions of the reaction it reacted further to form ketone **4**. To test this hypothesis we treated ketone **3** separately under the same conditions used in the base-catalyzed rearrangement of the dienol **1**, and indeed ketone **3** was observed to isomerize in the presence of base exclusively and quantitatively to ketone **4**. In order to definitely establish ketone **3** as an intermediate it was necessary to examine the following conditions governing this base-catalyzed rearrangement: base strength, temperature, and reaction time or reflux period (Table I).

TABLE I

EFFECT OF BASE, TEMPERATURE, AND REFLUX PERIOD ON THE REARRANGEMENT OF 1,2,3,4,5-PENTAPHENYL-2,4-CYCLOPENTADIEN-1-OL (1) TO 2,3,4,5,5-PENTAPHENYL-2-CYCLOPENTEN-1-ONE (4)

Base–solvent	Temp, °C	Time, hr	Yield of 4, %
NaOH–IAE[h]	173	8	90
NaOH–IAE	95	8	10[a]
NaOH–IAE	50	20	0[b]
NaOH–IAE	23	20	0[b]
Na_2CO_3–IAE	173	7	86[c]
$NaHCO_3$–IAE	173	7	80[d]
$NaNH_2$–IAE	173	8	90
HMPA	173	3	88[e]
HMPA	95	3	10[f]
N,N-DEF	173	3	66[g]

[a] Also obtained were 84% **1** and 6% **3**. [b] Quantitative recovery of **1**. [c] Also obtained were 11% **1** and 3% **3**. [d] Also obtained were 13% **1** and 7% **3**. [e] Also obtained were 10% **1** and 2% **3**. [f] Also obtained were 87% **1** and 3% **3**. [g] Also obtained were 27% **1** and 7% **3**. [h] Isoamyl ether.

As can be seen from Table I, the rearrangement of dienol **1** to ketone **4** proceeds with weak as well as with strong bases, and also in cases where the solvent used can act as a base. The overall effect of the base strength observed on this rearrangement was only on the rate of production of ketone **4**. The decrease in the rate of production of ketone **4** at 95° in either IAE or HMPA is believed to be due to the fact that higher temperatures are required to facilitate the phenyl migration,[1b] which is the first step in this overall rearrangement.

The effect of the reflux period was investigated by adding the dienol **1** as a solid all at once to a mixture of IAE and sodium hydroxide at 173° and taking samples

by syringe at various times (Table II) which were subjected to both infrared and glpc analysis. The sample

TABLE II
THE ISOMERIZATION REACTION OF 1,2,3,4,5-PENTAPHENYL-2,4-CYCLOPENTADIEN-1-OL IN ISOAMYL ETHER WITH SODIUM HYDROXIDE

Reaction time, min	% ratio Dienol 1	Ketone 3	Ketone 4
15	89.9	10.1	0.0
45	86.9	13.1	0.0
75	78.1	16.1	5.8
90	71.6	21.0	7.4
110	67.5	22.5	10.0
135	63.3	24.9	11.8
150	60.0	25.7	14.3
180	53.7	24.2	22.1
240	38.6	20.2	41.2
315	21.3	11.2	67.5
380	14.7	7.9	77.4
440	6.8	4.0	89.2
470	0.0	0.0	100.0

taken after 10 min showed only two products in the ir with peaks at 3500 and 1760 cm^{-1} corresponding to the dienol **1** and ketone **3**, respectively. This was borne out by glpc analysis which also showed only two peaks corresponding to the same compounds. However, analysis of all samples taken after 60 min and up to 455 min showed three distinct compounds to be present with peaks in the ir at 3500, 1760, and 1720 cm^{-1}, corresponding to the dienol **1**, ketone **3**, and ketone **4**, respectively. Analysis of these samples by glpc also showed three distinct peaks corresponding to the same three compounds. Using fractional crystallization techniques it was possible to isolate ketone **3** in pure form from each of these intermediate samples. Samples taken after 455 min all showed only one peak in both the ir and glpc, corresponding to ketone **4**. Plotting the ratio of the products obtained from glpc analysis *vs.* time (Figure 1) shows clearly that ketone **3** is produced during the reaction and that it then slowly disappears with increased reaction time.

Based upon the information obtained from this investigation the mechanism proposed for the base-catalyzed rearrangement of dienol **1** is shown in Scheme IV. One consideration which should be mentioned is that the electron density is not equally distributed at the various sites in anion **7**, but according to Pariser–Parr–Pople SCF π calculations the electron density should be distributed in the following order: O (1.58 e) > C_2 (1.32 e) > C_4 (1.27 e), placing the largest electron density on oxygen. Thus, owing to the differences in the distribution of the electron densities, one might expect to obtain ketone **3** as the major product of this reaction because protonation of the anion **7** should take place at the more electron-dense sites, oxygen, which produces enol **2** which tautomerizes to ketone **3**, and C_2, which produces ketone **3** directly, while ketone **4** is formed in only minor amounts from protonation at the least electron-dense site C_4. This would be the course of the reaction if anion **7** were being internally protonated and the products thus formed were unreactive. Figure 1 shows that this is indeed exactly the situation which occurs in the early stages of the reaction. This mechanism suggests that ketone **3** is the

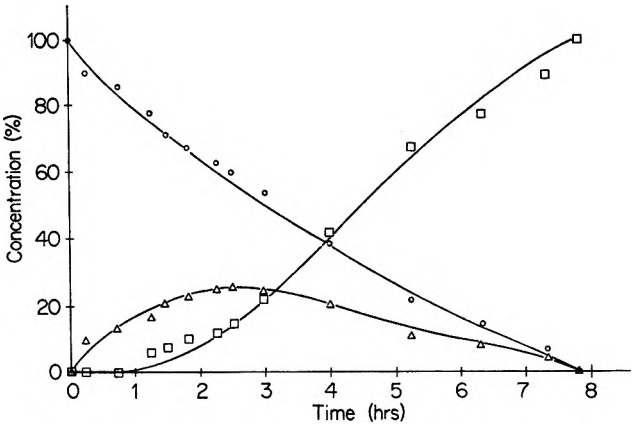
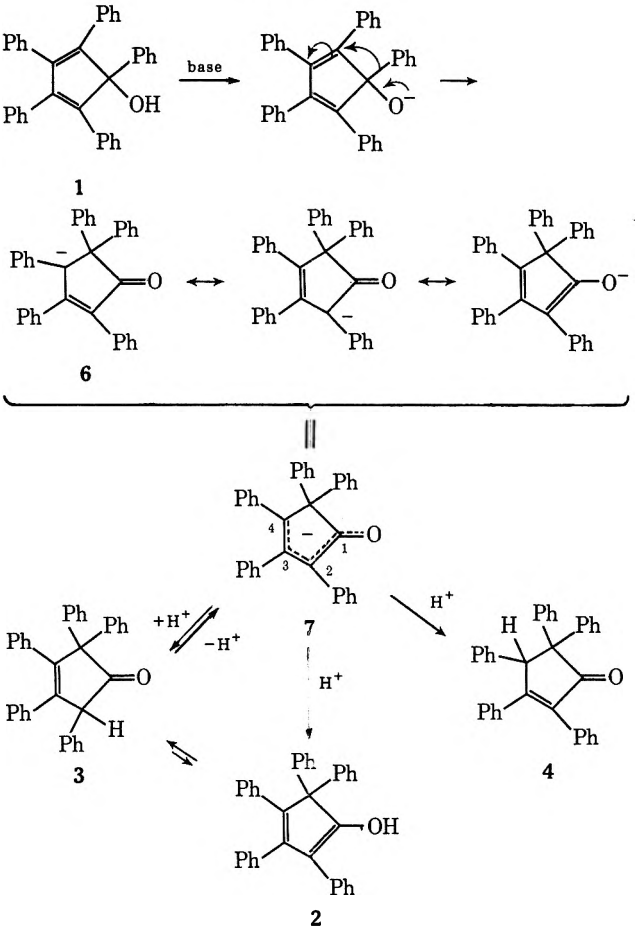


Figure 1.—Variation with time of the concentration of dienol **1**, ketone **3**, and ketone **4** at 173° in isoamyl ether with sodium hydroxide: ○, dienol **1**; △, ketone **3**; □, ketone **4**.

SCHEME IV



kinetically controlled product and ketone **4** the thermodynamically controlled product of this reaction.

There are three possible sources for internal protonation: the water formed from the reaction of the sodium hydroxide with the dienol **1**, the unreacted dienol **1** itself, and ketone **3** formed in the initial stages of the reaction. It appears that the water formed is not an important source of protons for the initial protonation process, because the minute amount of water formed could not survive long enough in the reaction medium owing to the high reaction temperature (173°), but that both the starting dienol **1** and the initially formed ketone **3** are the main sources of protons for the inter-

nal protonation process. To verify that the water formed does not play an important role in the protonation process, we investigated in detail the reaction of the dienol **1** with one of the bases previously mentioned, sodium amide. Treatment of the dienol **1** with a catalytic amount of sodium amide produced a small amount of anion **7** and ammonia. Following the path of this reaction by glpc analysis and comparing the results obtained with the reaction profile of the dienol **1** and sodium hydroxide gave exactly the same results with respect to the products produced and the intermediate observed; the absence of water did not in any way affect the product distribution. These observations also rule out the possibility of an external quenching mechanism taking place when the samples were removed from the reaction vessel and added to water, because, if external quenching were responsible for the formation of the products and there was no internal quenching of anion **7**, then the product distribution obtained should not be time dependent and the product ratio of ketone **3** to ketone **4** would be constant and time independent. This is contrary to what has been observed and thus the mechanism proposed in Scheme IV appears to be the most appropriate.

Experimental Section

Rearrangement of 1,2,3,4,5-Pentaphenyl-2,4-cyclopentadien-1-ol (1) to 2,3,4,5,5-Pentaphenyl-2-cyclopenten-1-one (4). I. In Isoamyl Ether (IAE) with Sodium Hydroxide. A. At 173°.—Into a 100-ml three-necked round-bottomed flask equipped with a reflux condenser and a magnetic stirrer was placed 50 ml of isoamyl ether and 3.0 g (75 mmol) of solid sodium hydroxide and the mixture was heated to the boiling point of the ether (173°). At this point 3.0 g (6.5 mmol) of 1,2,3,4,5-pentaphenyl-2,4-cyclopentadien-1-ol (1)[1a,4] was added as a solid all at once. The resulting mixture was refluxed for 8 hr, cooled to room temperature, and then poured into 100 ml of water. The organic layer was separated, washed several times with water, and dried over anhydrous magnesium sulfate and the solvent was removed under vacuum to afford a viscous yellow oil, which was crystallized from a mixture of benzene–petroleum ether (bp 30–60°) to give 2.7 g (5.8 mmol, 90%) of pale yellow crystals of 2,3,4,5,5-pentaphenyl-2-cyclopenten-1-one (**4**), mp 169–170° (lit.[1a,5] mp 169–170°). The ir,[5] uv,[5] and nmr[1a] spectral data for this compound agreed with the literature data.

The above experiment was repeated for glpc analysis using the same amount of material and essentially the same experimental set-up except that the flask was also equipped with a serum cap. Samples of 2 ml each were taken at various times (Table II) by inserting a hypodermic syringe through the serum cap. The samples thus removed were placed in separate containers and cooled by means of an ice–water bath. After all the required samples were collected, glpc analysis was carried out using a Bendix Model 2600 gas chromatograph and a Bendix Model 1200 recorder. The glpc was equipped with a 3 ft × 0.25 in. column packed with 3% QF-1 on Chromosorb W (H. P., mesh 100/120) support. Operating conditions were as follows: temperature of inlet, 210°; detector, 255°; injector, 255°; column, 210°; and a He carrier gas flow rate of 80 ml/min. Retention time of the dienol **1** was 6 min 15 sec; of the ketone **3**, 13 min 45 sec; and of the ketone **4**, 15 min 45 sec. Analysis of the peak areas observed were determined by triangulation[6] and the per cent composition represented by these peak areas was then calculated (Table II) and plotted on the same graph *vs.* time (Figure 1). Qualitative infrared analysis of each sample was also performed and for the sample taken after 10 min only two products were observed to be present, the dienol **1** with a hydroxyl peak at 3500 cm^{-1} and ketone **3** with a carbonyl peak at 1760 cm^{-1}. Analysis of all samples taken after 60 min and up to 455 min showed three distinct products to be present, the dienol **1** (hydroxyl peak at 3500 cm^{-1}), ketone **3** (carbonyl peak at 1760 cm^{-1}), and ketone **4** (carbonyl peak at 1720 cm^{-1}). Fractional crystallization techniques using varying mixtures of benzene–petroleum ether allowed separation and isolation of both ketone **3** and ketone **4** from each of these intermediate samples. The physical and spectral data for ketone **3** agreed with the literature.[1a] Analysis of samples taken after 455 min showed only one peak to be present in both the ir and glpc corresponding to ketone **4**. Crystallization of these samples from benzene–petroleum ether afforded 90–96% of ketone **4**, the deviation from 100% probably owing to losses during crystallization and isolation.

B. At Room Temperature (23°).—The above experiment was repeated using the same amount of material and the same experimental set-up except that the temperature used was room temperature. Analysis by both ir and glpc of samples taken in 2-hr intervals over a 20-hr period showed only the dienol **1** to be present. Work-up of the mixture after 20 hr afforded only recovered dienol **1** (99%).

C. At 50°.—Again the above experiment was repeated for 20 hr except that the temperature used was thermostatically maintained at 50 ± 1° by means of a constant-temperature oil bath. The results obtained were exactly the same as those described in B above except that work-up after 20 hr afforded a quantitative recovery of dienol **1**.

D. At 95°.—The above experiment was repeated for 8 hr, this time at a thermostatically controlled temperature of 95 ± 1°. Analysis by ir of the samples taken at 0.5-hr intervals during the 8-hr reaction period showed the presence of three distinct compounds after 1.5 hr, with peaks corresponding to dienol **1** (hydroxyl, 3500 cm^{-1}), ketone **3** (carbonyl, 1760 cm^{-1}),[1a,5,7] and ketone **4** (carbonyl, 1720 cm^{-1}).[1a,5] The composition of this mixture changed very slowly and continuously until after 8 hr glpc analysis still showed three compounds to be present, dienol **1** (84%), ketone **3** (6%), and ketone **4** (10%).

II. In Hexamethylphosphoramide (HMPA). A. At 173°.—Into a 100-ml, three-necked, round-bottomed flask equipped with a reflux condenser and a magnetic stirrer was placed 50 ml of HMPA, bp 90° (3 mm), which was heated to 173 ± 1° by a thermostatically controlled constant-temperature oil bath. At this temperature 1.8 g (3.9 mmol) of dienol **1** was added as a solid all at once, and the mixture was heated for 3 hr, cooled to room temperature, and poured into 100 ml of water. The aqueous solution was extracted twice with benzene, and the benzene solutions were combined, washed with water, dried over anhydrous magnesium sulfate, and concentrated to essential dryness on the rotoevaporator. The viscous yellow oil which resulted was taken up in carbon tetrachloride. A small sample of this solution was removed for glpc analysis while the rest was chromatographed on Woelm acid alumina using carbon tetrachloride as eluent. The first band which separated was collected, concentrated, and crystallized from benzene–petroleum ether, affording 1.5 g (3.2 mmol, 82%) of pale yellow crystals of ketone **4**, mp 169–170°. Further elution of the column with carbon tetrachloride, chloroform, and acetone followed by concentration and work-up did not afford any other organic material. Analysis of the sample removed from the carbon tetrachloride solution by glpc analysis showed 88% of ketone **4**, 10% of dienol **1**, and 2% of ketone **3** to be present.

B. At 95°.—The above experiment was repeated for 3 hr using a temperature of 95 ± 1° (thermostatically controlled) followed by work-up and chromatography. The first band eluted gave 10% of ketone **4**, while continued elution with carbon tetrachloride afforded a second band which upon concentration and crystallization from petroleum ether gave 87% of starting dienol **1**. Analysis by glpc of a sample removed before work-up showed 87% of dienol **1**, 10% of ketone **4**, and 3% of ketone **3**.

III. In *N,N*-Diethylformamide (*N,N*-DEF).—Using the same amount of dienol **1** as reported in IIA above, this experiment was performed as described above for 3 hr using 50 ml of *N,N*-DEF (bp 177–178°) thermostatically controlled at 173°. The product mixture was worked up and chromatographed as described in IIA to give 66% of ketone **4** and 27% of starting dienol **1**. Glpc analysis of a sample removed before work-up showed 27% of dienol **1**, 66% of ketone **4**, and 7% of ketone **3**.

IV. Using Sodium Carbonate and Bicarbonate.—Into a 100-ml, three-necked, round-bottomed flask equipped with a reflux

(4) K. Ziegler and B. Schnell, *Justus Liebigs Ann. Chem.*, **445**, 266 (1925).

(5) C. Dufraisse, G. Rio, and A. Ranjon, *C. R. Acad. Sci.*, **253**, 2441 (1961).

(6) As described in H. M. McNair and E. J. Bonelli, "Basic Gas Chromatography," Varian Associates, Palo Alto, Calif., 1969, p 154.

(7) R. Breslow and H. W. Chang, *J. Amer. Chem. Soc.*, **83**, 3727 (1961).

condenser and a magnetic stirrer was placed 50 ml of IAE and 2.0 g (19 mmol) of anhydrous sodium carbonate, and the mixture was heated to 173°. At this point 2.0 g (4.3 mmol) of dienol **1** was added as a solid all at once and the resulting mixture was heated at 173° for 7 hr. After this time a small sample was removed, worked up as previously described, and then chromatographed on Woelm acid alumina using carbon tetrachloride as eluent. The first band which was eluted afforded 1.7 g (3.7 mmol, 86%) of ketone **4**, while the second band gave 0.2 g (0.43 mmol, 10%) of recovered unreacted dienol **1**. Glpc analysis of the sample removed showed 10.4% of dienol **1**, 86.2% of ketone **4**, and 3.4% of ketone **3** to be present.

Repeating the above experiment but using sodium bicarbonate as the base afforded after work-up 1.6 g (3.4 mmol, 80%) of ketone **4** and 0.2 g (0.52 mmol, 12%) of dienol **1**. Glpc analysis of the sample removed showed 12.7% of dienol **1**, 80.5% of ketone **4**, and 6.8% of ketone **3**.

V. Using Sodium Amide.—Into a 100-ml, three-necked, round-bottomed flask equipped with a reflux condenser, a magnetic stirrer, a nitrogen inlet tube, and a serum cap was placed 40 ml of IAE which was heated to 173°. At this point a mixture of 0.008 g (0.2 mmol) of sodium amide and 1.0 g (2.2 mmol) of dienol **1** was added all at once. (Caution! This experiment should only be performed on a small scale and the stirring should be stopped until after the addition. Ammonia is liberated very vigorously at this temperature.) Samples of 1 ml each were taken at various times by inserting a hypodermic syringe through the serum cap. These samples were analyzed exactly the same as described in IA. Comparison of the glpc results obtained for these samples with the results obtained in IA showed them to be identical.

Rearrangement of 2,2,3,4,5-Pentaphenyl-3-cyclopenten-1-one (3) to 2,3,4,5,5-Pentaphenyl-2-cyclopenten-1-one (4) in Isoamyl Ether with Sodium Hydroxide.—Into a 100-ml, one-neck, round-bottomed flask equipped with a reflux condenser and a magnetic stirrer was placed 50 ml of IAE and 1.0 g (25 mmol) of sodium hydroxide and the mixture was heated to the boiling point of IAE (173°). At this temperature, 1.0 g (2.1 mmol) of ketone **3**[1a,b] was added as a solid all at once. The heterogeneous mixture was heated for 6 hr, cooled to room temperature, and poured into 100 ml of cold water, and the organic layer was separated, washed several times with 100-ml portions of water, and dried over anhydrous magnesium sulfate. Concentration of this dried solution under vacuum gave a viscous yellow oil which was crystallized from 50 ml of a mixture of benzene–petroleum ether to give a quantitative yield (1.0 g, 2.1 mmol) of pale yellow crystals of ketone **4**, mp 169–170° (lit.[1a,b] mp 169–170°).

Registry No.—**1**, 2137-74-8; **3**, 34759-47-2; **4**, 34759-48-3.

Acknowledgment.—We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Fluorinated Bicyclics. I. Exo-Cis-Bromination of Fluorinated Norbornenes[1]

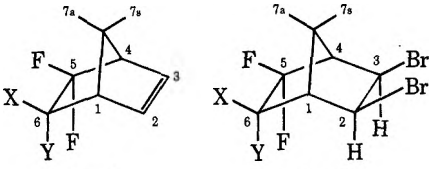
BRUCE E. SMART

Contribution No. 1984 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

Received November 10, 1972

A number of fluorinated norbornenes **1a–h** brominate stereospecifically by a purely radical pathway in methylene dichloride or carbon tetrachloride at 25° to afford exclusively exo-cis dibromides **2a–h**. The radical bromination of 5,5-difluoro-6-*exo*-fluoro-2-norbornene (**1i**) affords a 2.1:1.9 mixture of exo-cis dibromide **2i** and trans dibromide **9**. These results suggest that the stereochemistry of the reaction is directed by endo fluorine substituents. Bromination of 5,5,6,6-tetracyano-2-norbornene (**13**) and *endo-cis*-5,6-dichloro-2-norbornene (**14**) is similarly stereospecific. The nmr spectra of the trifluoronorbornenes **1h** and **1i** and the dibromides **2**, along with dehydrobromination results, are discussed.

The reaction of bicyclo[2.2.1]-2-heptene (norbornene) with molecular bromine in CH_2Cl_2 at 25° readily affords a plethora of rearrangement products characteristic of reactions involving norbornyl cation intermediates.[2] It was therefore surprising to find 5,5,6,6-tetrafluoro-2-norbornene (**1a**) inert under these conditions, although bromination readily takes place under radical conditions (illumination) to afford exclusively *exo-cis*-2,3-dibromo-5,5,6,6-tetrafluoronorbornane (**2a**). A number of fluorinated norbornenes have been prepared and brominated to further investigate the scope of this reaction.



1a–i **2a–i**

a, X = Y = F
b, X = Y = CF_3
c, X = Y = Cl
d, X = CF_3; Y = F
e, X = F; Y = CF_3
f, X = CF_2Cl; Y = Cl
g, X = Cl; Y = CF_2Cl
h, X = H; Y = F
i, X = F; Y = H

Results

Norbornene Syntheses.—The norbornenes **1a–i** are readily prepared from the cycloaddition of the appropriate fluoro olefin and cyclopentadiene. The cycloaddition of cyclopentadiene and hexafluoropropene has been reported, although no description of the isomeric product mixture was presented.[3] At 155° for 72 hr a 53:47 mixture of **1d,e** (by nmr) was obtained. The structure of the respective isomers could not be unambiguously assigned by nmr. These derivatives

(1) Presented in part at the 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 1972.

(2) (a) D. R. Marshall, J. R. Robinson, *et al.*, *Can. J. Chem.*, **49**, 885 (1971); (b) H. Kwart and L. A. Kaplan, *J. Amer. Chem. Soc.*, **76**, 4072 (1954).

(3) H. P. Braendlin, *et al.*, *J. Amer. Chem. Soc.*, **84**, 2112 (1962).

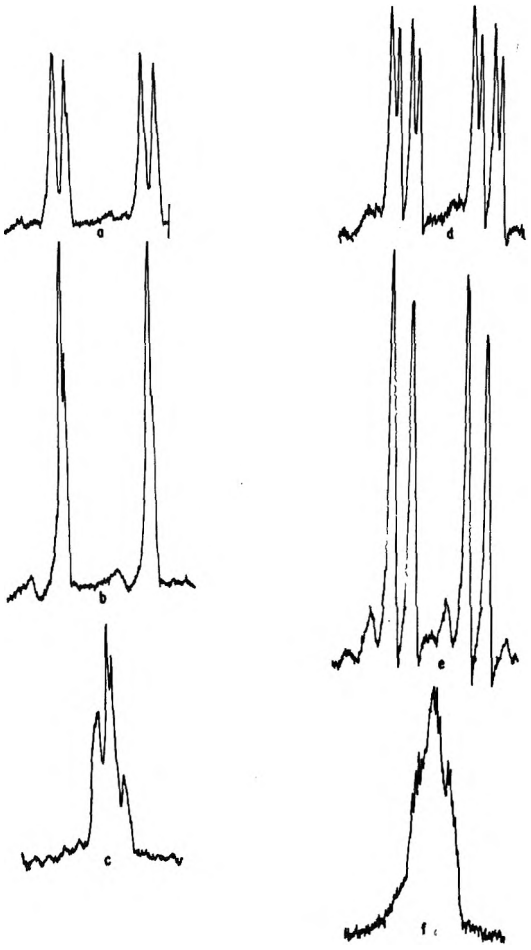
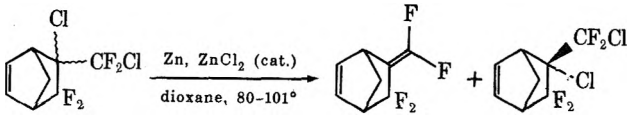


Figure 1.—^{19}F nmr spectra: a, F_{6n} in **1h**; b, F_{6n} upon H_{7s} irradiation; c, F_{6n} upon H_{6x} irradiation; d, F_{6x} in **1i**; e, F_{6x} upon H_1 irradiation; f, F_{6x} upon H_{6n} irradiation.

resisted separation by vpc and the bromination studies were performed on the **1d,e** mixture.

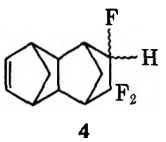
The cycloaddition of 2,3-dichlorotetrafluoropropene and cyclopentadiene at 155° for 48 hr gave a 3:2 mixture (76% yield) of norbornenes **1f,g**. These



1f,g **3** **1f**

isomers also resisted efficient separation by vpc. Partial dehalogenation of the 3:2 mixture (20 mequiv) with Zn in dioxane at 80° for 4 hr afforded a 1:1 mixture of olefin **3** and unreacted starting material which was a single isomer. Structure **1f** was tentatively assigned to the recovered isomer, which assumes a lower reactivity for the endo 5-chlorine in **1f** *vis-à-vis* the exo 5-chlorine in **1g**. Isomer **1f** was also the major Diels–Alder adduct.

Trifluoroethylene and cyclopentadiene at 155° for 72 hr afforded a 67:33 mixture of monoadducts **1h,i** in 72.5% yield based on consumed cyclopentadiene and diadduct **4** formation. The isomers were readily



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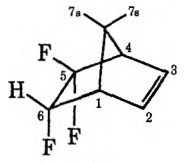
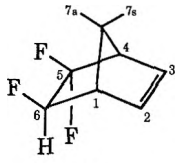
separable by vpc and the major isomer was assigned structure **1h** based on the following nmr data (see Table I).

TABLE I

CHEMICAL SHIFTS AND COUPLING CONSTANTS FOR 5,5-DIFLUORO-*endo*-6-FLUORO-2-NORBORNENE (**1h**) AND 5,5-DIFLUORO-*exo*-6-FLUORO-2-NORBORNENE (**1i**) IN CARBON TETRACHLORIDE



1h



1i

Chemical Shifts[a]

Nuclei	1h	Isomer 1i
H_2, H_3	6.28	6.24
H_1, H_4	3.06	2.93
H_{6x}	4.88	
H_{6n}		4.37
H_{7s}	1.80	2.00
H_{7a}	1.68	2.27
F_{6x}		191.4
F_{6n}	191.9	
F_{5x}	100.2	112.8
F_{5n}	113.6	102.8

Coupling Constants, Hz

Nuclei	1h	Isomer 1i
$H_{7a}H_{7s}$	10.5	11
H_1F_6		5.7
$H_{6x}F_{5x}$	17	
H_6F_6	55.0	55.1
$H_{6n}F_{5n}$		~9.5
$H_{7s}F_{6n}$	6.5	
$F_{6x}F_{5x}$		12.5
$F_{5x}F_{5n}$	234	234

[a] All proton chemical shifts are reported in parts per million (δ) relative to internal tetramethylsilane. All fluorine chemical shifts in parts per million (ϕ) relative to fluorotrichloromethane (F-11) internal standard. All values refer to the high-field side of F-11.

The ^{19}F nmr spectrum of **1i** displayed a doublet (J = 55.1 Hz) of doublets (J = 12.5 Hz) of doublets (J = 5.7 Hz) at ϕ 191.4 for F_6 (Figure 1c) and an AB quartet of multiplets for F_{5x} and F_{5n} (J_{AB} = 234 Hz). Nucleus A (ϕ 102.8) was further split into a doublet of multiplets ($J \cong$ 9.5 Hz) as was nucleus B (J = 12.5 Hz). Double-resonance experiments assigned the 55.1-Hz splitting to the geminal F_6H_6 coupling and the 5.7-Hz splitting resulted from coupling of the H_1 bridgehead proton to F_6 (Figure 1e,f). The exo stereochemistry of F_6 was therefore established. The 12.5-Hz splitting, which was undisturbed by proton–fluorine decoupling, was assigned to the $F_{5x}F_{6x}$ coupling.

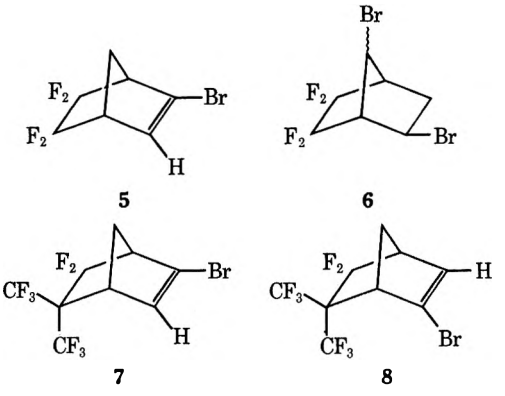
For **1h**, F_6 appeared as a doublet (J = 55.0 Hz) of doublets (J = 6.5 Hz) at ϕ 191.9 (see Figure 1a) and F_{5x} and F_{5n} gave an AB quartet of multiplets (J_{AB} = 234 Hz) with nucleus A (ϕ 100.2) further split into a doublet (J = 17 Hz) of multiplets and B (ϕ 113.6) split into a triplet ($J \cong$ 4 Hz) of multiplets. Selective decoupling experiments established that H_6 and F_6 were coupled (55.0 Hz) and a long-range coupling (6.5 Hz) of F_6 and H_{7s} was present (Figure 1b,c). The 17-Hz splitting was assigned to $H_{6x}F_{5x}$ coupling.

The H_{6n} proton in **1i** appeared as a doublet (J_{HF} = 55.1 Hz) of doublets (J_{HF} = 9.6 Hz) of doublets (J = 2.4 Hz) at δ 4.37 in the pmr spectrum (Figure 2). In **1h**, H_{6x} was at a lower field (δ 4.88) as a doublet (J_{HF} = 55.0 Hz) of doublets (J_{HF} = 17 Hz) of doublets (J = 4 Hz). These observations are consistent with the usual upfield shift of endo 5,6 protons relative to exo 5,6 protons in 5,6-halogenated 2-norbornenes.[4-7]

The unreliability of structure assignment based on fluorine chemical shifts of exo and endo fluorines in this system should be emphasized. Roberts and coworkers found a consistent pattern of upfield chemical shift of the endo relative to the exo fluorine in a number of saturated *gem*-difluoronorbornanes.[8] However, recent work by Homer and Callaghan on fluorinated norbornenes demonstrated that the shielding effects were reversed relative to the saturated systems.[9] In the trifluoronorbornenes **1h** and **1i** F_{6n} is slightly upfield (0.5 ppm) relative to F_{6x}, and in **1h** F_{5n} is upfield (13.4 ppm) from F_{5x}, which is in accord with Robert's observations. In contrast, F_{5x} appears upfield (10 ppm) to F_{5n} for **1i** in agreement with Homer and Callaghan. These relative shift deviations suggest substantial sensitivity toward the vicinal neighboring group.

Bromination Studies.—The olefins **1a–i** were inert to molecular bromine in CCl_4 or CH_2Cl_2 at 25° in the dark under oxygen. Bromination was instantaneous at 25° in a nitrogen atmosphere when the reaction mixture was illuminated with a 275-W sun lamp. Small-scale runs in CCl_4 were examined by nmr and vpc. Quantitative conversion to a single dibromide product (>98%) was indicated for **1a–h**. Preparative scale runs were performed in CH_2Cl_2 solvent at 25° in a nitrogen atmosphere. Vpc and nmr analysis again indicated the formation of a single product and the crude product was isolated in >90% yield in all cases.

The dibromide isolated from **1a** was assigned structure **2a** based on chemical and spectroscopic evidence. Dehydrobromination of the dibromide product with potassium *tert*-butoxide in ether afforded a single elimination product, assigned structure **5**. The nmr



5 6

7 8

spectrum of **5** exhibited a single vinyl proton resonance at δ 6.35. Hence, structure **6** is eliminated as a possible dibromide product. The vicinal protons H_2, H_3 in **2a** appeared as a sharp doublet (J = 1.8 Hz) at δ 4.58. A double-resonance experiment established the methylene bridge proton H_{7a} (δ 2.05) as the source of this splitting. The cis-exo stereochemistry of the vicinal bromides in **2a** therefore was established.

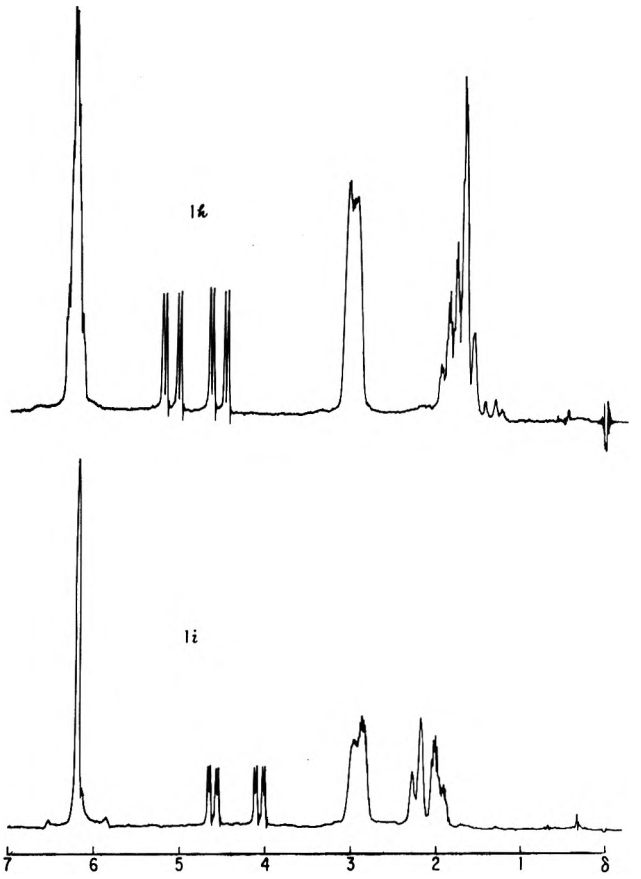


Figure 2.—Nmr spectrum (100 MHz) of 5,5-difluoro-5-*endo*-fluoro-2-norbornene (**1h**) and 5,5-difluoro-6-*exo*-fluoro-2-norbornene (**1i**).

The dibromide structures **2b–h** were confirmed by nmr. The vicinal H_2, H_3 protons appeared as an AB quartet of multiplets in each case with J_{H_2,H_3} = 6.9–7.0 Hz (Table III). The magnitude of this coupling is consistent with a cis orientation of the vicinal protons.[4,5,10-13] The AB quartets were further split by 1.7–1.9 Hz from the methylene bridge proton H_{7a}. Figures 3a–d display typical AB multiplets for dibromides **2b**, **2c**, **2h**, and **2f** + **2g**.

Dehydrobromination of **2b** with potassium *tert*-butoxide in ether at 25° afforded an 11.5:1 mixture of products **7** and **8**. A sharp resonance at δ 6.53 (1 vinyl hydrogen) was present in the nmr of the product mixture.

The bulky *endo*-trifluoromethyl group at C_5 is anticipated to provide substantial steric hindrance toward approach of the large *tert*-butoxide base at H_{2n}. Base therefore attacks the more sterically accessible proton H_{3n} in **2b** to give predominantly **7**.

The norbornenes **1h** and **1i** displayed a similar reluctance to brominate in CH_2Cl_2 or CCl_4 in the dark.

(4) P. Laszlo and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1171 (1963).
(5) P. Subramanian, M. T. Emerson, and N. A. Le Bel, *J. Org. Chem.*, **30**, 2624 (1965).
(6) R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).
(7) J. Paasivirta, *Suom. Kemistilehti B*, **36**, 76 (1963).
(8) J. B. Grutzner, J. D. Roberts, *et al.*, *J. Amer. Chem. Soc.*, **93**, 7107 (1970).
(9) J. Homer and D. Callaghan, *J. Chem. Soc. B*, 2430 (1971).
(10) F. L. Anet, H. H. Lee, and J. L. Submeier, *J. Amer. Chem. Soc.*, **89**, 4431 (1967).
(11) S. J. Cristol and B. B. Jarvis, *J. Amer. Chem. Soc.*, **89**, 5885 (1967).
(12) C. L. Osborne, T. V. Van Auken, and D. J. Trecker, *J. Amer. Chem. Soc.*, **90**, 5806 (1968).
(13) A. G. Ludwick and J. C. Martin, *J. Org. Chem.*, **34**, 4108 (1969).

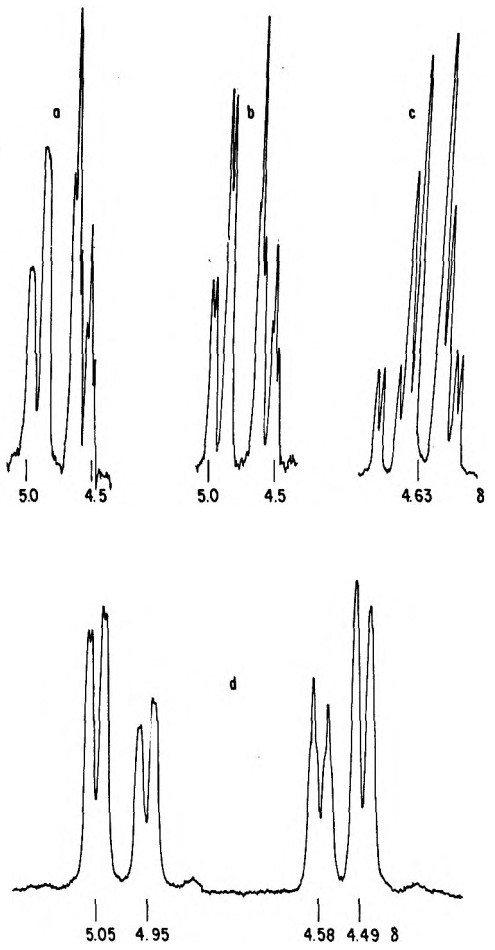
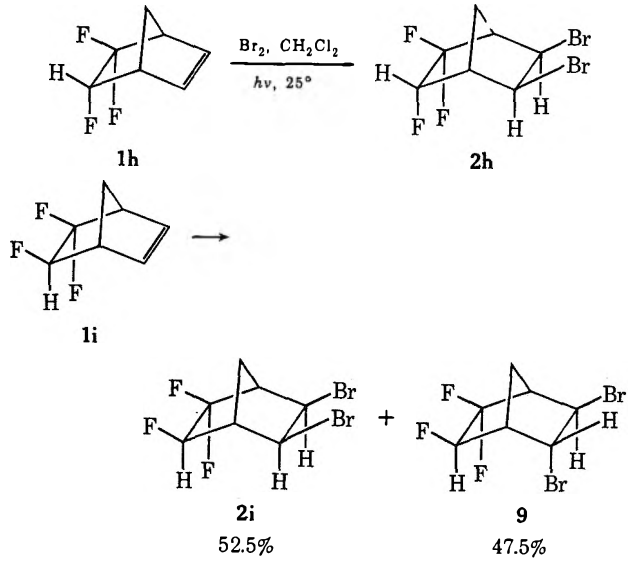


Figure 3.—Nmr spectrum of vicinal H_2, H_3 protons: a, compound **2b** (60 MHz); b, compound **2c** (60 MHz); c, compound **2h** (220 Mz); d, 3:2 mixture of **2f** and **2g** (220 mHz).



Irradiation during bromination in a nitrogen atmosphere induced immediate and quantitative conversion of **1h** to **2h**, whereas **1i** afforded a 1.1:1 mixture of dibromides **2i** and **9**, respectively.[14] Structures **2h** and **2i** were readily confirmed by their characteristic AB quartets with J_{AB} = 6.9–7.0 for protons H_2, H_3

(14) Dibromides **2i** and **9** were both stable under the reaction and vpc conditions. This mixture therefore represents the kinetically controlled product distribution.

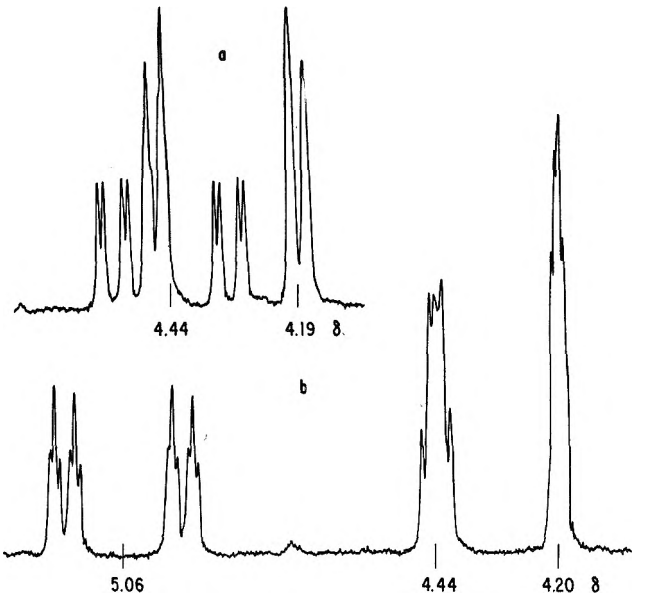
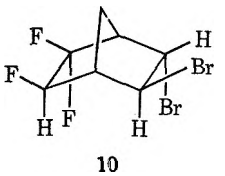


Figure 4.—Nmr spectra (220 MHz) of vicinial H_2, H_3, and H_6 protons: a, compound **2i**; b, compound **9**.

(Figures 3c, 4a; Tables II and III). The dibromide **9**, separated from **2i** by preparative vpc, gave a markedly different nmr pattern for the vicinal protons H_2, H_3 (Figure 4b). Two different multiplets appear at δ 4.20 and 4.44 with the downfield proton split into approximately a doublet ($J \cong 3.8$ Hz) of triplets ($J \cong 3.2$ Hz), whereas the upfield proton gave a much narrower resonance. Long-range H_2F_{6x} coupling gave rise to the 3.8-Hz splitting. A doublet of doublets with $J_{H_2H_1} \cong J_{H_2H_3} \cong 3.2$ Hz gave the fortuitous triplet pattern. These splitting patterns suggest exo stereochemistry for one downfield proton (δ 4.44). The 3.2-Hz vicinal H_2H_3 coupling is indicative of trans stereochemistry;[4,5,12,13] hence, the upfield proton (δ 4.20) is endo.

A comparison of the relative chemical shifts of the proton H_{6n} geminal to fluorine in **2i** and **9** illustrates an interesting deshielding effect. Proton H_{6n} in **9** (δ 5.06) was shifted appreciably downfield (0.62 ppm) relative to H_{6n} in **2i**. This suggests that the bromine substituent at C_2 is endo and a deshielding proximity effect is operable.[15,16] The alternative trans isomer **10** cannot account for this shielding.



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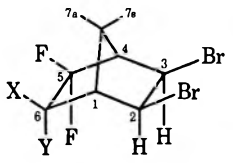
Dehydrobromination of **9** with *tert*-butoxide in ether afforded a single product containing one vinyl proton (δ 6.16), whereas **2i** gave a 4:1 mixture of elimination products. The major product proved to be identical with that obtained from **9**. The minor product also exhibited a single vinyl proton resonance (δ 6.18).

(15) Laszlo and Schleyer (ref 4) have observed a similar proximity effect in 5-halogenated 2-norbornenes. Introduction of an exo 5-chlorine substituent causes a downfield shift (*ca.* 0.4 ppm) of the anti 7-proton relative to norbornene itself. A slight upfield shift (0.05–0.1 ppm) is produced by endo 5-chlorine substitution.

(16) (a) G. S. Reddy and J. H. Goldstein, *J. Chem. Phys.*, **38**, 2736 (1963); (b) R. F. Zürcher, *J. Chem. Phys.*, **37**, 2421 (1962).

TABLE II

CHEMICAL SHIFTS[a] FOR DIBROMONORBORNANES IN CARBON TETRACHLORIDE



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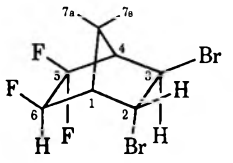


9

Dibromide	H_2 H_3	H_1 H_4	H_{7a}[b]	H_{7s}[b]	X	Y	F_{5x}[b]	F_{5n}[b]	
2a, X = Y = F	4.58	2.96	2.05	2.47	118.6	122.4	118.6		122.4
	d	t of m	m	t of m	br t	br d			
2b, X = Y = CF_3	(4.57, 4.92)[c]	2.94	2.8–3.3[d]		64.4	60.8	99.1		114.2
	AB q of m	m	m		d of q	d of q of d	q of m		br q of m
2c, X = Y = Cl	(4.34, 4.62)	(3.01, 3.22)	2.32	2.57			94.7		106.5
	AB q of m	d of m, m	m	d of m			m		d of m
2d,e[e] X, Y = CF_3, F	(4.51, 4.74)	2.59	(2.08, 2.28)		75.6 d of d of d of	179.8 m		(109.9, 117.6)	
	AB q of m	2.93–3.16[d]			171.2 m	72.9 d of d of d		(111.5, 118.0)	
2f, X = CF_2Cl; Y = Cl	(4.49, 5.05)	(2.98, 3.18)	2.38	2.64	54.4, 57.2			(104.8, 105.6)	
	AB q of m	m	m	d of m	AB q of m				
2g, X = F; Y = CF_2Cl	(4.58, 4.95)[f]								
	AB q of m								
2h, X = H; Y = F	(4.58, 4.66)	(2.89, 2.99)	1.69	2.39	4.63	203.5	98.2		121.8
	AB q of m	d of m, m	m	t of m	d of d of d	d of d	d of d		d of m
2i, X = F; Y = H	(4.19, 4.47)	2.85	2.21	2.41	194.4	4.44	111.3		116.5
	AB q of m	m	m	m	d of br t	d of d of d	d of m		m
9	4.44, 4.20	2.77	2.22	2.30	204.5	5.06		114.2[d]	
	d of d of d[g] m	m	m	m	br d	d of d of t		m	

[a] See Table I, footnote *a*. [b] AB q of m for $H_{7a}H_{7s}$ and $F_{5x}F_{5n}$ in each case. [c] Values in parentheses indicate that the respective chemical shifts are unassigned. [d] Individual resonances not resolved. [e] Determined in a mixture of **2d** and **2e** (respective isomers unknown). [f] Determined in a 3:2 mixture of **2f** and **2g**, other assignments not possible owing to overlapping resonances. [g] Appears as a d of t.

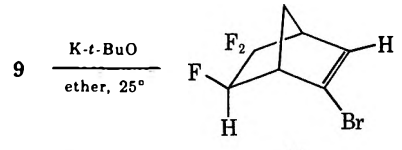
TABLE III

COUPLING CONSTANTS (HERTZ) FOR DIBROMONORBORNANES IN CARBON TETRACHLORIDE

Dibromide	H_2H_3	$H_{7s}H_{7a}$	H_2H_{7a}[a]	$F_{5x}F_{5n}$	$H_{7s}F_{5n}$	Miscellaneous
2a		12.5	1.8	241	5.3	$H_1H_{6x} \sim 5$
2b	7.0		1.7	255		$CF_{3x}CF_{3n} = 13.5$, $F_{5n}CF_{3n} = 23$, $F_{5x}CF_{3x} = 19.5$
2c	7.0	13	1.8	224	4.9	
2d,e[b]	6.9		1.7–1.9	252	6–7	$(CF_3)_xF_{6n} = 14$, $(CF_3)_xF_{5x} = 8$
	6.9			254		$(CF_3)_nF_{6x} = 14$–15, $(CF_3)_xF_{5n} = 8$
2f	6.9	14	1.9			$(CF_AF_BCl)_x = 172$
2g[c]	6.9					
2h	7.0	12		248	7	$H_6F_6 = 53$, $H_6F_{5x} = 19.5$, $H_4F_{5x} \sim 6.5$, $F_6H_{7a} \sim 8$
2i	6.9	12		251		$H_6F_6 = 51$, $H_6F_{5n} = 10.6$, $F_6F_{5x} \sim 9.5$
9	~3.2	12				$H_6F_6 = 51.3$, $H_6F_{5n} = 8.3$, $H_{2x}F_{6x} \sim 3.8$, $H_{2x}H_1 \sim 3.2$

[a] $H_2H_{7a} = H_3H_{7a}$ (±0.1 Hz) for **2a**–**i**. [b] Respective isomer assignments not made; see Table II, footnote *e*. [c] See Table II, footnote *f*.

Dibromide **9** allows for facile exo-cis coplanar elimination[17] of $H_{2x}Br_{3x}$ and the exclusive product is assigned structure **11**. Only trans elimination is possible



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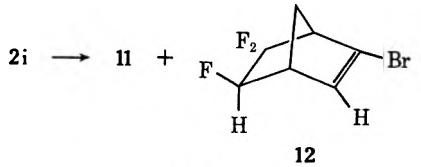

12

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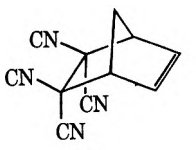
for **2i**, and the product distribution reflects the ease of *tert*-butoxide approach at C_2 *vs.* C_3. The endo fluorine substituent at C_5 provides sufficient interference (*vide infra*) toward approach of base at H_{3n} that elimination of H_{2n} is preferred. The minor dehydrobromination product therefore is assigned structure **12**.

The tetracyanoethylene adduct **13** brominated only under radical conditions to afford exclusively **15**. The



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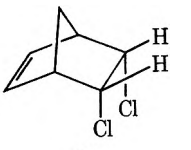

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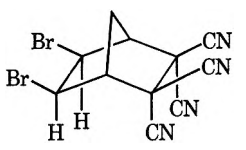

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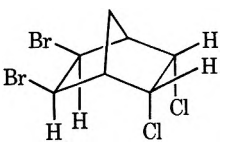


16

reaction of the endo-cis dichloride **14** with bromine in CH_2Cl_2 at 25° was very sluggish under ionic conditions, although bromination was instantaneous under radical conditions. The cis-exo dibromide was the only product formed. Structures **15** and **16** were readily established by nmr. Both **15** and **16** displayed sharp

(17) J. Sicher, *Angew. Chem., Int. Ed. Engl.*, **11**, 200 (1972), and references cited therein.

doublets with $J_{H_{2,3}H_{7a}}$ = 2.2 and 2.0 Hz, respectively, for the vicinal endo-cis protons.

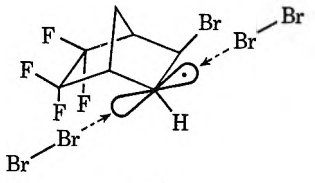
Discussion

The electron-withdrawing γ substituents clearly exert an appreciable deactivating influence on the norbornene double bond. Ionic bromination of norbornene proceeds smoothly at even −78°, whereas **1a–i** failed to brominate under similar ionic conditions at 25°. A very facile free-radical bromination pathway, however, has been demonstrated at 25°.

This deactivation of the norbornene double bond is not unique to γ-fluorine substitution; the γ-cyano- and γ-chloro-substituted norbornenes **13** and **14** are similarly unreactive.[18]

The stereospecificity of the free-radical brominations of **1a–h** is striking. Free-radical additions of large addenda to norbornene itself generally proceed to give predominantly trans adducts. For example, CCl_4,[12] CCl_3Br,[19] n-C_3F_7I,[20] and CBr_3F[13] give >95% trans addition. Free-radical chlorination of norbornene gives 38% trans and 34% cis addition.[21] Although the stereospecificity of free-radical bromination of norbornene itself has not been studied in detail, it has been suggested that addition is preferentially trans.[2a,22] The highly stereospecific cis-bromination of **1a–h** is unanticipated and demands further examination.

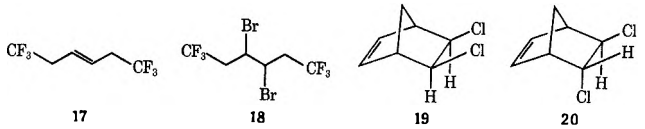
The free-radical bromination of olefin **1a** first involves addition from the less hindered exo side, which is unexceptional for bulky attacking groups,[12,23] to afford **20**. The direction of subsequent attack on **20**



20

by the propagating bromine molecule is determined by the relative nonbonded interactions with the 2-exo-bromo substituent and the 5,6-endo substituents.[24]

(18) The primary mode of transmission of the γ-substituent inductive effect is a moot point. A "through bond" or "through space" (field effect) mechanism may be operative. 1,4-Bis(trifluoromethyl)-2-butene (**17**) displays unreactivity similar to that of **1a** toward ionic bromination. Free radical bromination at 25° affords a 1.16:1 mixture of *erythro*-**18**–*threo*-**18**.



17 **18** **19** **20**

Whereas **14** is very sluggish toward ionic bromination, both **19** and **20** brominate, albeit very slowly relative to norbornene itself, under ionic conditions. The latter observations suggest the importance of a field effect (B. E. Smart, unpublished results).

(19) E. Tobler and D. J. Foster, *J. Org. Chem.*, **29**, 2839 (1964).

(20) N. O. Brace, *J. Org. Chem.*, **27**, 3027 (1962).

(21) M. L. Poutsma, *J. Amer. Chem. Soc.*, **87**, 4293 (1965).

(22) The exo-cis dichloride **19** (footnote 18) gives *ca.* 90% trans dibromide under radical conditions in CH_2Cl_2 at 25° in contrast to exclusive cis-exo addition to **14** (B. E. Smart, unpublished results).

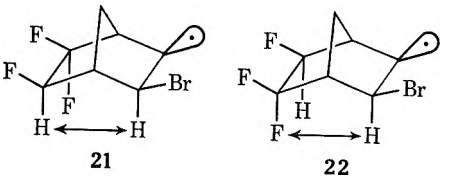
(23) For a recent review of the subject, see D. I. Davies and S. J. Cristol in "Advances in Free Radical Chemistry," Vol. I, G. H. Williams, Ed., Logos Press, London, 1965, Chapter 5.

(24) This discussion uses compound **1a** as an example throughout, although similar arguments follow for **1b–h**.

For norbornene itself, the less hindered path is from the endo direction with trans product formation.

The observed exo-cis product from **1a** suggests that the endo 5,6-fluorine substituents effectively shield **20** from endo approach. The introduction of bulky 5,6-endo substituents is known to direct attack to the exo side in the free addition of polyhalomethanes to norbornene.[12,13] Although the difference in steric size of fluorine and hydrogen is small, nonbonded repulsion between fluorine with its tight sphere of outer core electrons and an electron-rich species in close approach is more severe than for hydrogen which lacks nonbonding electrons.[25] Approach of bromine from the endo side in **20** is unfavorable owing to coulombic repulsion from the endo fluorine substituents, so that the normally hindered exo attack becomes more facile. Similar effects are exhibited by endo chlorine and nitrile substituents in the brominations of **13** and **14**.

The trifluoronorbornene **1i** demonstrates a case in which only one endo fluorine substituent is present. Attack of bromine on **1i** can afford either **21** or **22**.



21 **22**

Based on the nearly equivalent amounts of cis (**2i**) and trans (**9**) products formed (1.1:1), the endo fluorine substituent exerts little influence on the initial attack by bromine. Attack at C_2 or C_3 is differentiated sterically only by the endo,endo repulsions of H_{2n},H_{6n} *vs.* H_{2n},F_{5n}, which result from movement of the olefin hydrogen to an endo position as sp^3 development at the carbon attacked proceeds. The carbon atom which accommodates the odd electron retains its sp^2 configuration and little change in geometry is anticipated. The small difference in 1,3-H,F *vs.* 1,3-H,H repulsion may account for the slight preference of attack at C_2 leading to **21**.[26] The influence of the endo fluorine on the stereochemistry of chain transfer, however, is significant. Attack on the carbon p orbital in **21** proceeds from the exo direction as in **20**. However, in **22** attack along the p-orbital axis from the endo direction is hindered by only an endo proton and predominantly trans product **9** results.

Dehydrobromination of **2i** with *tert*-butoxide also illustrates this endo-fluorine shielding effect. Approach of base at H_{3n} is repulsed by the 5-endo fluorine substituent, whereas approach at H_{2n} involves interaction with only an endo proton H_{6n}. The preference for **11** formation reflects these factors.

The fluorine substituent, although relatively small in size, can nonetheless significantly control the stereospecificity of chemical reactions. The recognition of potential coulombic interactions provides a reasonable explanation for these observations.

(25) See B. E. Smart, *J. Org. Chem.*, **38**, 2035 (1973), for further discussion of this point.

(26) Similar arguments were presented by Osborne and coworkers (ref 12) to explain the effect of *endo*-5-methyl substitution on the stereochemistry of free-radical addition of carbon tetrachloride to norbornene.

Experimental Section

Proton nmr spectra were recorded on Varian Associates A-60, HA-100, or HR-220 MHz spectrometers. ^{19}F nmr spectra were determined on a Varian Associates A56-60 or a HA-100 spectrometer operating at either 56.4 or 100 MHz. The proton–fluorine decoupling experiments were performed on the HA-100 spectrometer with fluorotrichloromethane (F-11) as a lock (9.3 kHz upper side band signal) by selective irradiation of the proton spectra with the basic radiofrequency provided by a Schomandl Synthesizer. All compounds were run as 20–30% solutions in CCl_4 or $CDCl_3$ with either tetramethylsilane (TMS) or F-11 as an internal reference. All chemical shifts are reported in parts per million downfield from TMS and upfield from F-11.

All melting and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237 spectrometer and the gas chromatography work was performed on a Varian Aerograph Series 200 gas chromatograph fitted with a Brown Potentiometer recorder. The following columns were used: column A, 6 ft × 0.375 in. 20% QF 1 fluorosilicone on 60/80 Chromosorb P; column B, 6 ft × 0.375 in. 20% silicone 200 on 60/80 Chromosorb W; column C, 6 ft × 0.375 in. 25% diglyceride on Gas-Chrom R; column D, 6 ft × 0.375 in. 25% Triton X305 on Chromosorb W; column E, 5 ft × 0.25 in. 3% SE-30 on 100/120 Aeropak 30.

Commercially available samples of tetrafluoroethylene, trifluoroethylene, perfluoroisobutylene (PFIB), perfluoropropene (PFP), and 1,1-dichlorodifluoroethylene were used directly without further purification. 2,3-Dichlorotetrafluoropropene was prepared following the reported literature procedures from commercially available 1,3-dichlorotetrafluoroacetone.[27] Freshly cracked cyclopentadiene was used in all cases for the cycloadditions. The olefins **1a**,[28] **1c**,[29] and **14**[30] were prepared by literature procedures. Freshly sublimed **1a** and preparative vpc samples of **1c** (column D, 125°) were employed. Olefin **14** was recrystallized from *n*-hexane prior to use. All olefins employed in the bromination studies were >99% pure by vpc.

5,5-Difluoro-6,6-bis(trifluoromethyl)-2-norbornene (1b).—Two 250-ml thick-walled Carius tubes, each charged with 25 g (0.125 mol) of PFIB, 6.6 g (0.1 mol) of cyclopentadiene, and 0.5 g of hydroquinone, were heated at 155° for 48 hr. The unreacted PFIB was distilled off, and the semisolid residues were combined and sublimed (80 mm, 25°) to afford 30.3 g of material composed of 87% **1b** and 13% dicyclopentadiene by nmr and vpc (column B, 100°). Fractional distillation afforded material of bp 88° (100 mm) which still contained *ca.* 10% dicyclopentadiene. This material was dissolved in CH_2Cl_2 and "titrated" with bromine in the dark. Removal of the solvent and resublimation (80 mm, 25°) afforded pure **1b** as a waxy, colorless solid: mp 82–84°; ir (CCl_4) 1550 cm^{-1} (very weak, C=C); nmr (CCl_4) ^1H δ 1.86, 2.61 (AB m of m, 2, J_{AB} = 11 Hz, A, d of m, $J \cong 5$ Hz), 3.12 (broad s, 1), 3.30 (broad s, 1), 6.38 (narrow m, 2); ^{19}F φ 59.7 (p of m, 3, J = 16, ~5 Hz), 64.1 (p of m, 3, $J \cong 16$ Hz), 97.3, 100.4 (AB m of m, 2, J_{AB} = 246 Hz, B, q of m, J = 16 Hz).

Anal. Calcd for $C_9H_6F_8$: C, 40.62; H, 2.27. Found: C, 40.68; H, 2.21.

5,5,6-Trifluoro-6-(trifluoromethyl)-2-norbornenes (1d and 1e).—A mixture of 78 g (0.52 mol) of PFP, 35 g (0.53 mol) of cyclopentadiene, and 1.8 g of hydroquinone was heated at 155° for 72 hr in a 500-ml bomb. Nmr of the reaction mixture indicated a 52.7:47.3 mixture of products. Fractionation *in vacuo* afforded 78.4 g (70%) of a 53:47 mixture of **1d** and **1e**: bp 63° (50 mm) (lit.[3] bp 140–140.5°); nmr (CCl_4 mixture) ^1H δ 1.7–2.5 (unresolved AB m of m, 2), 4.82 (m, 2), 6.27 (minor), 6.33 (major) (narrow m, 2); ^{19}F (major isomer) φ 77.9 (complex m, 3), 107.8, 108.8 (AB m of m, 2), 170.8 (broad m, 1); ^{19}F (minor isomer) 74.7 (q, 3, J = 7.2 Hz), 107.8 109.0 (AB m of m, 2), 170.2 (broad m, 1). Isomers **1d** and **1e** could not be separated by vpc (columns A–C).

5,5-Difluoro-6-(chlorodifluoromethyl)-6-chloro-2-norbornenes (1f and 1g).—A 500-ml bomb charged with 100 g (0.547 mol) of 2,3-dichlorotetrafluoropropene, 33 g (0.5 mol) of cyclopentadiene, and 0.5 g of hydroquinone was heated at 155° for 48 hr. Fractional distillation afforded 94.6 g (76%) of a 3:2 mixture of **1f** and **1g**: bp 87–88° (20 mm); nmr (CCl_4) ^1H (major isomer) δ 1.97, 2.37 (AB m of m, 2, J_{AB} = 10.5 Hz), 3.18 (broad m, 1), 3.45 (broad m, 1), 6.44 (sharp m, 2); ^{19}F (major isomer) φ 53.7, 56.7 (AB m of m, 2, J_{AB} = 172 Hz, A, d of m, J = 18.5 Hz, B, d of m, J = 22.5 Hz); 93.1, 105.6 (AB m of m, 2, J_{AB} = 230 Hz, B, broad t of m, $J \cong 21$ Hz); ^{19}F (minor isomer) 52.4 (broad t, 2, $J \cong 20$ Hz), 87.0, 103.7 (AB m of m, 2, J_{AB} = 228 Hz, B, broad t of m, $J \cong 20$ Hz).

Anal. Calcd for $C_8H_6Cl_2F_4$: C, 38.59; H, 2.43; Cl, 28.49. Found: C, 38.75; H, 2.45; Cl, 28.89.

Attempted vpc separation of **1f** and **1g** on column C, 115°, gave a 43:7 mixture. The major product was that of the original 3:2 mixture.

5-(Difluoromethylene)-6,6-difluoro-2-norbornene (3).—A solution of 24.9 g (0.1 mol) of **2f** and **2g** (3:2 mixture) in 25 ml of dry dioxane was added dropwise to a well-stirred slurry of 50 g of Zn dust in 175 ml of refluxing dioxane containing 0.5 g of anhydrous $ZnCl_2$. After complete addition, the mixture was allowed to reflux for an additional 16 hr in an N_2 atmosphere. After cooling to room temperature the mixture was filtered; the filtrate was quenched in 300 ml of cold H_2O and extracted with CH_2Cl_2. The organic extract was washed with H_2O and saturated aqueous NaCl, and finally dried ($MgSO_4$). Fractionation afforded 11.8 g (94% conversion, 71% yield) of **3**: bp 54–55° (50 mm); ir (CCl_4) 1777 cm^{-1} (C=CF_2); nmr (CCl_4) ^1H δ 1.95 (s, 2), 3.09 (broad m, 1), 3.48 (broad m, 1), 6.20, 6.46 (AB m of m, 2, $J_{AB} \cong 6$ Hz); ^{19}F φ 87.6, 88.7 (AB m of m, 2, J_{AB} = 48 Hz, B, q of m, $J \cong 5$ Hz), 99.3, 104.9 (AB m of m, 2, J_{AB} = 232 Hz).

Anal. Calcd for $C_8H_6F_4$: C, 53.94; H, 3.40. Found: C, 53.61; H, 3.34.

Further distillation gave 1.4 g (6%) of **1f**, bp 67° (7 mm). A similar reaction with 5.0 g (20 mmol) of **1f** and **1g** (3:2), 10 g of Zn dust, and 50 mg of anhydrous $ZnCl_2$ catalyst in 50 ml of dry dioxane at 80° for 4 hr afforded a 1:1 mixture of **3**:**1f** by nmr. No **1g** (>2%) was present.

5,5,6-Trifluoro-2-norbornenes (1h and 1i).—A mixture of 164 g (2.0 mol) of trifluoroethylene, 66 g (1.0 mol) of cyclopentadiene, and 1 g of hydroquinone was heated at 155° for 72 hr in a 1-l. bomb. Fractionation afforded a mixture (57.4 g) of 67% **1h** and 33% **1i**, bp 86–90° (170 mm), and 32.8 g of **4**, bp 88–90° (4 mm). The high-boiling pot residue, 11.8 g, contained mostly tricyclopentadienes. An analytical sample of **4** (mixture of isomers) was collected by preparative vpc (column B, 175°): nmr (CCl_4) δ 0.82 broad doublet (half of AB m, 1, J = 12 Hz), 1.15–1.60 (AB m of m, 2), 1.9–2.25 (complex m, 7), 4.42 (d of d of d, 1, J = 54, 19.5, ~4.5 Hz), 6.05 (m, 2); ^{19}F (major isomer) φ 98.2, 124.3 (AB m of m, 2, J_{AB} = 234 Hz, A, d of d of m, J = 19.5, 8.2 Hz), 205.0 (d of d of d, 1, J = 54, 9.5, ~4.5 Hz); ^{19}F (minor isomer) 116.0 (m, 2), 193.8 (d of m, 1, J = 54 Hz).

Anal. Calcd for $C_{12}H_{13}F_3$: C, 67.28; H, 6.12. Found: C, 67.25; H, 6.11.

Preparative vpc (column C, 115°) afforded pure **1h**, mp 76–77.5°, ir (CCl_4) 1583 (very weak C=C), 1660 cm^{-1} (weak), and **1i**, mp 71–73°, ir (CCl_4) 1579 (very weak C=C), 1647 cm^{-1} (weak).

Anal. Calcd for $C_7H_7F_3$: C, 56.76; H, 4.76. Found (**1h**): C, 57.01; H, 4.58. Found (**1i**): C, 56.53; H, 4.86.

Brominations. General Procedures.—Small-scale runs were performed in an nmr tube by the dropwise addition of molecular bromine to *ca.* 20% solutions of the appropriate norbornene in CCl_4 under illumination with a 275-W sun lamp. Bromine uptake was instantaneous in all cases. No bromine uptake was evident when the reactions were run in the dark. The reactions were run to *ca.* 75% completion and examined by nmr and vpc.

Preparative-scale runs were performed at 25° with degassed CH_2Cl_2 solvent under a nitrogen atmosphere. A 275-W sun lamp *ca.* 6 in. from the reaction vessel was employed. After the complete addition of bromine (1–1.1 equiv), illumination was continued for an additional 5 min. The reaction mixture was then washed with 5% aqueous sodium thiosulfate and saturated NaCl, and finally dried ($MgSO_4$). Vpc analysis showed complete conversion of starting olefin in each case. The CH_2Cl_2 solvent was removed on a rotary evaporator (25–40°) to afford the crude dibromide product.

***exo-cis*-2,3-Dibromo-5,5,6,6-tetrafluoronorbornane (2a).**—Treatment of 8.3 g (50 mmol) of **1a** in 45 ml of CH_2Cl_2 with 8.2 g (51.3 mmol) of bromine in 5 ml of CH_2Cl_2 afforded a quantitative yield of crude **2a** (>99%), mp 57–59°. Recrystallization from hexane afforded pure **2a**, mp 58.0–58.5°.

(27) J. E. Bissey, H. Goldwhite, and D. G. Rousell, *J. Org. Chem.*, **32**, 1542 (1967).

(28) J. J. Drysdale, *et al.*, *J. Amer. Chem. Soc.*, **80**, 245, 3672 (1959).

(29) P. D. Bartlett, L. K. Montgomery, and B. Seidel, *J. Amer. Chem. Soc.*, **86**, 616 (1964).

(30) D. D. Tanner and G. C. Gidley, *J. Org. Chem.*, **33**, 38 (1968).

Anal. Calcd for $C_7H_6Br_2F_4$: C, 25.80; H, 1.86; Br, 49.02. Found: C, 25.73; H, 1.80; Br, 48.81.

exo-cis-2,3-Dibromo-5,5-difluoro-6,6-bis(trifluoromethyl)norbornane (2b).—Addition of 12.8 g (0.08 mol) of bromine in 10 ml of CH_2Cl_2 to 20 g (0.075 mol) of **1b** in 90 ml of CH_2Cl_2 afforded 33 g (99%) of crude **2b** (>98%). Sublimation (20 mm, 65°) gave 26.2 g (78.5%) of pure **2b**, mp 59.5–61.5°.

Anal. Calcd for $C_9H_6Br_2F_8$: C, 25.38; H, 1.42; Br, 37.52. Found: C, 25.63; H, 1.46; Br, 37.07.

exo-cis-2,3-Dibromo-5,5-difluoro-6,6-dichloronorbornane (2c).—The reaction of 1.99 g (10 mmol) of **1c** in 10 ml of CH_2Cl_2 with 1.7 g (10.6 mmol) of bromine in 2 ml of CH_2Cl_2 afforded 3.41 g (95%) of **2c** (>98%). Recrystallization from petroleum ether (bp 40–60°) afforded pure **2c**, mp 48.5–50°.

Anal. Calcd for $C_7H_6Br_2F_2Cl_2$: C, 23.43; H, 1.69; Cl, 19.76. Found: C, 23.67; H, 1.65; Cl, 20.09.

exo-cis-2,3-Dibromo-5,5,6-trifluoro-6-(trifluoromethyl)norbornane (2d and 2e).—Treatment of 21.6 (0.1 mol) of **1d** and **1e** (53:47) in 100 ml of CH_2Cl_2 with 17.6 g (0.11 mol) of bromine in 15 ml of CH_2Cl_2 afforded 35.5 g (97%) of crude **2d** and **2e** (>98%). Distillation afforded 32.4 g (86%) of pure product, bp 77–78° (5 mm) [lit.[31] bp 92–93° (10 mm)]. The isomeric dibromides **2d,e** could not be separated by vpc. The chemical shifts of H_{2n}, H_{3n} in the isomers were indistinguishable at 220 MHz in CCl_4.

exo-cis-2,3-Dibromo-5,5-difluoro-6-(chlorodifluoromethyl)-6-chloronorbornane (2f and 2g).—Bromination of 20 g (0.08 mol) of **1f** and **1g** (3:2) in 90 ml of CH_2Cl_2 with 13 g (0.081 mol) of bromine in 10 ml of CH_2Cl_2 afforded 31.7 g (97%) of crude **2f** and **2g** (>98%, 3:2 by 220-MHz nmr). Distillation gave 28.7 g (88%) of pure product, bp 84–86° (0.7 mm).

Anal. Calcd for $C_8H_6Br_2Cl_2F_4$: C, 23.50; H, 1.48; Cl, 17.34. Found: C, 23.68; H, 1.45; Cl, 17.71.

exo-cis-2,3-Dibromo-5,5-difluoro-*endo*-6-fluoronorbornane (2h).—Bromination of 3.00 g (20.3 mmol) of **1h** in 30 ml of CH_2Cl_2 with 3.25 g (20.6 mmol) of bromine in 10 ml of CH_2Cl_2 afforded 5.80 g (92%) of crude **2h** (>95%). A pure sample of **2h** was obtained by preparative vpc (column A, 170°), mp 29.5°.

Anal. Calcd for $C_7H_7Br_2F_3$: C, 27.30; H, 2.29. Found: C, 27.56; H, 2.45.

exo-cis-2,3-Dibromo-5,5-difluoro-*exo*-6-fluoronorbornane (2i) and *endo*-2-Bromo-*exo*-3-bromo-5,5-difluoro-*exo*-6-fluoronorbornane (9).—Bromination of 6.00 g (40.6 mmol) of **1i** with 6.57 g (41.2 mmol) of bromine as for **2h** afforded 11.87 g (95%) of 52.5% **2i** and 47.5% **9** (vpc, column A, 175°). Pure **2i**, mp 48–50°, and **9** (an oil) were collected by preparative vpc (column A, 165°).

Anal. Calcd for $C_7H_7Br_2F_3$: C, 27.30; H, 2.29. Found (**2i**): C, 27.18; H, 2.48; (**9**) C, 27.47; H, 2.25.

Irradiation (275-W sun lamp) of small samples of pure **2i** and **9** in CH_2Cl_2 containing bromine had no effect. The isomers were stable to the vpc conditions (165–175°).

exo-cis-2,3-Dibromo-5,5,6,6-tetracyanonorbornene (15).—A solution of 5.82 g (30.0 mmol) of **13** in 175 ml of CH_2Cl_2 was treated dropwise with a solution of 5.60 g (31.1 mmol) of bromine in 10 ml of CH_2Cl_2. After *ca.* 75% bromine addition, a white solid precipitated from the reaction mixture. The reaction mixture was filtered after complete addition and the filter cake was washed with cold CH_2Cl_2 to afford 6.96 g (62%) of **15**, mp 270–271° dec. Work-up of the filtrate gave an additional 3.26 g (29%) of **15**. Recrystallization from benzene afforded pure **15**: mp 270° dec; ir (Nujol mull) 2330 cm^{-1} (very weak, CN); nmr (acetone-d_6) δ 2.45, 2.90 (AB m of m, 2, J_{AB} = 13.4 Hz, B, t of m, J = 1.5 Hz), 3.94 [t (1.5 Hz), 2], 4.96 (d, 2, J = 2.2 Hz).

Anal. Calcd for $C_{11}H_6Br_2N_4$: C, 37.32; H, 1.71; N, 15.83. Found: C, 37.21; H, 1.43; N, 15.67.

exo-cis-2,3-Dibromo-*endo-cis*-5,6-dichloronorbornane (16).—Bromination of 8.2 g (0.05 mol) of **14** in 65 ml of CH_2Cl_2 with 8.5 g (0.053 mol) of bromine in 10 ml of CH_2Cl_2 gave >98% **16** by vpc (column E, 180°). Work-up afforded 14.5 g (89.5%) of white solid, mp 158–159°. Recrystallization from hexane–benzene (6:1) afforded pure **16**: mp 158–159°; nmr ($CDCl_3$) δ 1.62, 2.53 (AB m of m, 2, J_{AB} = 11.8 Hz, B, t of m, J = 1.9 Hz), 2.90 (m, 2), 4.41 [t (2.1 Hz), 2], 4.88 (d, 2, J = 2.0 Hz).

(31) E. McBee, *et al.*, *J. Amer. Chem. Soc.*, **77**, 915 (1955). This reference includes a number of brominated norbornenes, although no stereochemistry is reported.

Anal. Calcd for $C_7H_5Br_2Cl_2$: C, 26.04; H, 2.50; Br, 49.50; Cl, 21.96. Found: C, 26.40; H, 2.31; Br, 49.86; Cl, 21.99.

Dehydrobrominations. General Procedures.—The appropriate dibromide was dissolved in ether and a slight excess of dry potassium *tert*-butoxide was added in portions. All operations were performed in an N_2 atmosphere. The heterogeneous reaction mixture was allowed to stir for 16 hr, quenched in cold water, dried ($MgSO_4$), and analyzed by vpc. Removal of the ether solvent on a rotary evaporator (25°) gave the crude product, which was examined by nmr. Small amounts ($\leq$5%) of *tert*-butoxide substitution products were evident in each case but were not further examined.

2-Bromo-5,5,6,6-tetrafluoro-2-norbornene (5).—A mixture of 34.6 g (0.10 mol) of **2a** and 11.5 g (0.103 mol) of potassium *tert*-butoxide in 500 ml of ether gave a single dehydrobromination product (vpc ,column A, 110°) after 16 hr. Examination of the crude product by nmr indicated *ca.* 16% of unreacted **2a**. Fractionation of the crude product afforded 17.2 g of **5**: bp 160° (10 mm); ir (neat) 1588 cm^{-1} (C=C); nmr (CCl_4) ^1H δ 2.12, 2.54 (AB m of m, 2, J_{AB} = 10.5 Hz), 3.11 (m, 2), 6.35 (m, 1); ^{19}F ϕ 113.7, 115.3 (AB m of m, 2, J_{AB} = 228 Hz). Starting material **2a**, 5.6 g, bp 64–65° (2 mm), was also recovered.

Anal. Calcd for $C_7H_5BrF_4$: C, 34.32; H, 2.06; Br, 32.67. Found: C, 34.42; H, 2.05; Br, 32.18.

2-Bromo-6,6-difluoro-5,5-bis(trifluoromethyl)-2-norbornene (7).—The reaction of 22.3 g (0.05 mol) of **2b** with 6.00 g (0.0535 mol) of potassium *tert*-butoxide in 250 ml of ether afforded 17.2 g (94.5%) of crude product. Vpc analysis (column B, 100°) indicated a mixture of 92% **7** and 8% **8**. Distillation afforded 13.7 g of the same mixture of **7** and **8**: bp 48–51° (4 mm); ir (neat) 1590 cm^{-1} (C=C); nmr (CCl_4) ^1H δ 2.19, 2.46 (AB m of m, 2, $J_{AB} \cong$ 11.5 Hz), 3.22 (m, 1), 3.38 (m, 1), 6.53 (sharp m, 1); ^{19}F ϕ 57.3 (m, 3), 95.3 ,106.8 (AB m of m, 2, J_{AB} = 251 Hz, B, q of m, $J \cong$ 20.5 Hz).

Anal. Calcd for $C_9H_5BrF_8$: C, 31.33; H, 1.46; Br, 23.16. Found: C, 31.52; H, 1.53; Br, 22.56.

2-Bromo-5,5-difluoro-*exo*-6-fluoro-2-norbornene (11).—A mixture of 726 mg (2.36 mmol) of **9** and 290 mg (2.6 mmole) of potassium *tert*-butoxide in 12 ml of ether afforded pure **11** by vpc (column A, 125°). No ureacted **9** was present. An analytical sample of **11** was collected (vpc, column A, 125°) as an oil from the crude product (4.42 mg, 82.6%): ir (neat) 1588 cm^{-1} (C=C); nmr (CCl_4) ^1H δ 2.18 (m, 2), 2.93 (m, 2), 4.45 (d of d of m, 1, J = 53, 9 Hz), 6.16 (d of d, J = 3.5, ~0.6 Hz); ^{19}F ϕ 102.9, 111.2 (AB m of m, 2, J_{AB} = 234 Hz, A, d of m, J = 9 Hz, B, d of m, $J \cong$ 10 Hz), 193.5 (d of d of m, 1, J = 53, 10 Hz).

Anal. Calcd for $C_7H_7BrF_2$: C, 37.03; H, 2.66. Found: C, 36.90; H, 2.46.

3-Bromo-5,5-difluoro-*exo*-6-fluoro-2-norbornene (12) and 11.—The procedure for **11** with 975 mg (3.16 mmol) of **2i** and 37 mg (3.3 mmol) of base in 15 ml of ether afforded 614 mg (85.7%) of crude product. Vpc analysis (column A, 125°) indicated that two products were present in a 4:1 ratio with respective retention times of 6.6 and 9.5 min. The individual products were collected by preparative vpc. The major product (6.6 min) was identical with **11** (vpc retention times, nmr, ir). The minor product (9.5 min) was identified as **12**: ir (neat) 1590 cm^{-1}; nmr (CCl_4) ^1H δ 2.23 (m, 2), 2.93 (m, 2), 4.45 (d of d of m, 1, J = 53, 9 Hz), 6.18 (d of d, J = 3.2, 1.3 Hz); ^{19}F ϕ 102.9, 111.3 (AB m of m, 2, J_{AB} = 236 Hz, A, d of m, J = 9 Hz, B, d of m, $J \cong$ 10.5 Hz), 193.6 (d of d of m, 1, J = 53, ~10.5 Hz).

Anal. Calcd for $C_7H_6BrF_3$: C, 37.03; H, 2.66. Found: C, 36.99; H, 2.51.

Registry No.—**1a**, 2822-56-2; **1b**, 39037-71-3; **1c**, 1643-76-1; **1d**, 39037-24-6; **1e**, 39004-83-6; **1f**, 39037-25-7; **1g**, 39037-26-8; **1h**, 37580-00-0; **1i**, 37579-98-9; **2a**, 39037-29-1; **2b**, 39037-30-4; **2c**, 39037-31-5; **2d**, 39004-84-7; **2e**, 39037-32-6; **2f**, 39037-33-7; **2g**, 39037-34-8; **2h**, 39037-35-9; **2i**, 39037-36-0; **3**, 39037-72-4; **4**, 39037-73-5; **5**, 39037-74-6; **7**, 39037-75-7; **9**, 39037-37-1; **11**, 39037-38-2; **12**, 39037-39-3; **13**, 6343-21-1; **14**, 2843-35-8; **15**, 39037-41-7; **16**, 39037-42-8; PFIB, 382-21-8; cyclopentadiene, 542-92-7; PFB, 116-15-4; 2,3-dichlorotetrafluoropropene, 684-04-8; trifluoroethylene, 359-11-5.

Acknowledgments.—The author is indebted to Dr. Derick Ovenall, Mr. Donald Nickerson, Mr. Lou Rizzardi, and Mr. Lou Walther for invaluable aid in obtaining the nmr spectra. Useful and stimulating discussion with Dr. Frank J. Weigert is also acknowledged. The reluctant ionic bromination of certain γ-fluorine substituted olefins was originally brought to my attention by Dr. James E. Nottke.

Fluorinated Bicyclics. II. Steric Control in the Free-Radical Addition of Polyhalomethanes to 5,5,6,6-Tetrafluoro-2-norbornene

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Received November 10, 1972

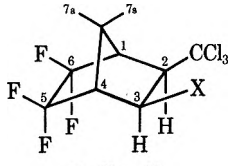
The free-radical addition of carbon tetrachloride, bromotrichloromethane, and *n*-heptafluoropropyl iodide to 5,5,6,6-tetrafluoro-2-norbornene (1) gave cis and trans adducts in the ratios of 2.7:1, 2.1:1, and 1:3.8, respectively. These results contrast with norbornene itself, where 95–100% trans addition is observed, and suggest that the endo fluorine substituents play a dominant role in directing the stereochemistry of these additions.

In a previous paper, the importance of endo fluorine coulombic effects in the stereospecific cis-exo-bromination of 5,5,6,6-tetrafluoro-2-norbornene (1) and related compounds was demonstrated.[1] The free-radical additions of carbon tetrachloride,[2] bromotrichloromethane,[2b] and *n*-heptafluoropropyl iodide[3] to norbornene itself are known to afford >95% trans adduct in each case. In order to investigate the influence of fluorine substitution, a detailed comparative study of the free-radical addition of these polyhalomethanes to 5,5,6,6-tetrafluoro-2-norbornene (1) was undertaken.

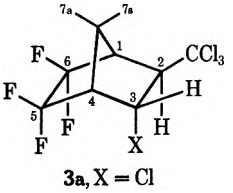
Results

The benzoyl peroxide initiated addition of carbon tetrachloride to **1** at 80° afforded a mixture of 73% cis **2a** and 27% trans **3a** adducts in 72% yield as well as

1



2a, X = Cl
b, X = Br



3a, X = Cl
b, X = Br

a substantial amount of telomeric residue. A similarly initiated reaction between **1** and bromotrichloromethane at 104° gave a mixture of 68% **2b** and 32% **3b** in 84% yield. Control experiments indicated that there was no product interconversion under either the reaction or vpc analytical conditions.

The 100-MHz nmr spectra of adducts **2a** and **3a** are shown in Figures 1a and 1b, and chemical shifts and coupling constants are tabulated in Tables I and II. Appropriate double-resonance experiments allowed for the assignment of long-range couplings. The spectra of **2b** and **3b** were quite similar to those of **2a** and **3a**, respectively, and the same analysis was applicable.

TABLE I

CHEMICAL SHIFTS[a] FOR POLYHALOMETHANE ADDUCTS IN CARBON TETRACHLORIDE

Nucleus	2a	2b	4	3a	3b	5
H_1H_4	3.09, 2.91	(3.06)[b]	3.18, 2.94	(2.99)	(3.03)	(2.90)
H_{2n}	3.52	3.48	~3.0[c]	3.42	3.40	3.05
H_3	4.58	4.56	4.36	4.28	4.26	4.21
H_{7a}	2.04	2.09	2.15	1.98	1.96	1.86
H_{7s}	2.73	2.76	2.45	2.36	2.40	1.91
F_{5x}	120.5	120.4	*c*	110.9	110.6	*c*
F_{5n}	126.5	126.7	*c*	118.0	117.7	*c*
F_{6x}	119.0	118.5	*c*	119.9	119.8	*c*
F_{6n}	119.3	119.0	*c*	126.0	125.6	*c*

[a] All proton chemical shifts are reported in parts per million (δ) relative to internal tetramethylsilane. All fluorine chemical shifts are in parts per million (φ) relative to fluorotrichloromethane (F-11) internal standard. All values refer to the high-field side of F-11. [b] Values in parentheses indicate that the H_1, H_4 protons were not resolved. [c] Could not be determined accurately owing to interferences.

TABLE II

COUPLING CONSTANTS (HERTZ) FOR POLYHALOMETHANE ADDUCTS IN CARBON TETRACHLORIDE

Nuclei	2a	2b	4	3a	3b	5
H_2H_3	6.9	7.1	7.8	6.9	6.7	7.8
$H_{7a}H_{7a}$	12.5	12.5	12–13	12.5	12	13
$H_{3x}H_4$				3.7	~4	
$H_{3x}F_{5x}$				3.7	~4	
$H_{7s}F_{5n}$				5.7	5.7	
$H_{7s}F_{6n}$	5.7	5.8		5.7	5.7	
$F_{5x}F_{5n}$	228	228		241	240	
$F_{6x}F_{6n}$				226	230	

The vicinal H_2, H_3 protons in **3a** appeared as an AB quartet of multiplets at δ 3.42 and 4.28. The downfield resonance was assigned to the proton geminal to chlorine, H_3, which was further split into an apparent triplet (J = 3.7 Hz). The next higher field resonance was assigned to the proton adjacent to the trichloromethyl group. Double-irradiation experiments indicated that proton H_3 was coupled to both bridgehead proton H_4 and fluorine F_{5x} by 3.7 Hz. The presence and magnitude of these couplings indicate that H_3

(1) B. E. Smart, *J. Org. Chem.*, **38**, 2027 (1973).
(2) (a) C. L. Osborne, T. V. Van Auken, and D. J. Trecker, *J. Amer. Chem. Soc.*, **90**, 5806 (1968). (b) E. Tobler and D. J. Foster, *J. Org. Chem.*, **29**, 2839 (1964).
(3) N. O. Brace, *J. Org. Chem.*, **27**, 3027 (1962).

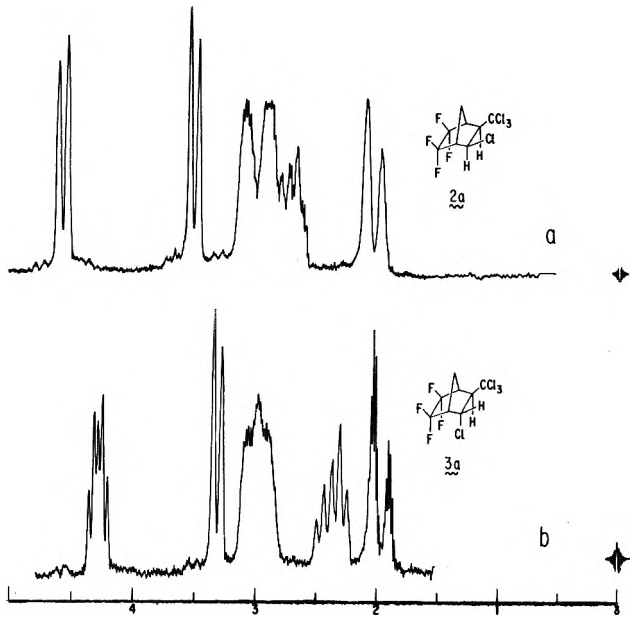
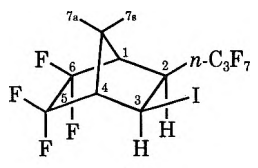


Figure 1.—Nmr (100 MHz) spectrum: a, *exo*-2-trichloromethyl-*exo*-3-chloro-5,5,6,6-tetrafluoronorbornane (**2a**); b, *exo*-2-trichloromethyl-*endo*-3-chloro-5,5,6,6-tetrafluoronorbornane (**3a**).

is exo. Proton H_2 gave a sharp resonance, suggestive of an endo proton. Simultaneous irradiation of H_4 and F_{5x} revealed an AB quartet for H_2, H_3 (Figure 2) with a coupling constant J_{H_2,H_3} = 6.9 Hz. This vicinal trans coupling constant is anomalously large and is normally observed for cis vicinal proton couplings in these systems.[2a,4-8]

The nmr spectrum of compound **2a** (Figure 1a) was analyzed similarly. The vicinal H_2, H_3 protons again appear as an AB quartet with J_{H_2,H_3} = 6.9 Hz. The magnitude of this coupling is consistent with a cis orientation for the vicinal protons. Neither the downfield proton H_3 adjacent to chlorine at δ 4.58 nor proton H_2 adjacent to trichloromethyl at δ 3.52 was coupled to H_1 or H_4 by the expected value of *ca.* 4 Hz, and the lack of appreciable coupling for these protons suggests that both H_2 and H_3 are endo.[9]

The benzoyl peroxide initiated addition of *n*-heptafluoropropyl iodide to **1** gave a mixture of 21% cis adduct **4** and 79% trans adduct **5** in 95% yield.



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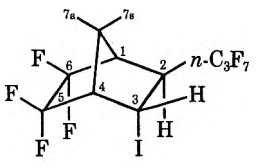


5

The 220-MHz nmr spectra of **4** and **5** are shown in Figures 3 and 4. These nmr spectra were much more difficult to interpret owing to extensive H–F couplings between proton H_2 and the adjacent perfluoroalkyl group. Unfortunate overlap of H_2 and the bridgehead

(4) P. Lazslo and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **84**, 2112 (1962).
(5) P. Subramanian, M. T. Emerson, and N. A. LeBel, *J. Org. Chem.*, **30**, 2624 (1965), and references cited therein.
(6) F. L. Anet, H. H. Lee, and J. L. Submeier, *J. Amer. Chem. Soc.*, **89**, 4431 (1967).
(7) S. J. Cristol and B. B. Jarvis, *ibid.*, **89**, 5885 (1967).
(8) A. G. Ludwick and J. C. Martin, *J. Org. Chem.*, **34**, 4108 (1969).
(9) The similarity of the vicinal H_2, H_3 nmr resonances in **2a** and *exo*-2-trichloromethyl-*exo*-3-chloronorbornane (**6**) (ref 2a) should be noted.

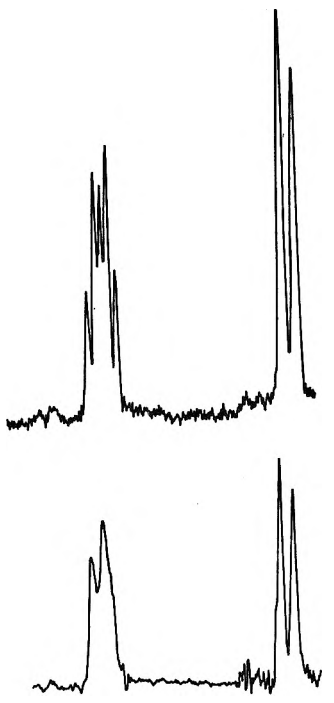


Figure 2.—Vicinal H_2, H_3 protons in **3a** (top); H_2, H_3 upon irradiation of H_4 and F_{5x} (bottom).

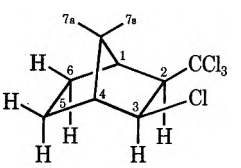
protons H_1 and H_4 further complicated analysis. However, a general comparison of the downfield H_3 proton patterns of **2**, **3** and **4**, **5** suggested the appropirate stereochemistry for **4** and **5**.

The proton adjacent to iodine, H_3 in **4**, appeared as approximately a doublet (half of an AB quartet) at δ 4.36 with J_{H_2,H_3} = 7.8 Hz. The lack of appreciable further coupling and the similarity with the downfield proton resonance shapes in **2a** and **2b** indicate that this proton is endo. The H_3 proton in **5** was a broad multiplet at δ 4.21, suggestive of an exo proton.

The proton adjacent to heptafluoropropyl in **5** appeared as an apparent doublet of triplets at δ 3.05. This pattern can be interpreted as a doublet (J = 7.8 Hz) of doublets (J = 23 Hz) of doublets (J = 7.8 Hz) with a vicinal coupling of 7.8 Hz and vicinal couplings of the nonequivalent methylene fluorines of the *n*-heptafluoroalkyl group with H_{2n} of 7.8 and 23 Hz. The anomalous equivalence of cis and trans vicinal proton couplings, which was observed for **2a,b** and **3a,b**, is apparent in the *n*-heptafluoropropyl iodide adducts as well.

A comparison of the chemical shifts of the protons adjacent to halogen indicates that the endo proton is downfield from the exo proton by 0.15–0.30 ppm. The opposite has been observed for 2,3-dihalogenated norbornanes.[5]

The proton chemical shifts for **2a**, **3a**, and the carbon tetrachloride adducts of norbornene **6** and **7** are com-



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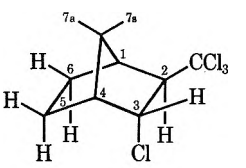

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pared in Table III. The H_{2n}, H_{3n} protons in the fluorinated derivatives **2a**, **3a** are markedly deshielded

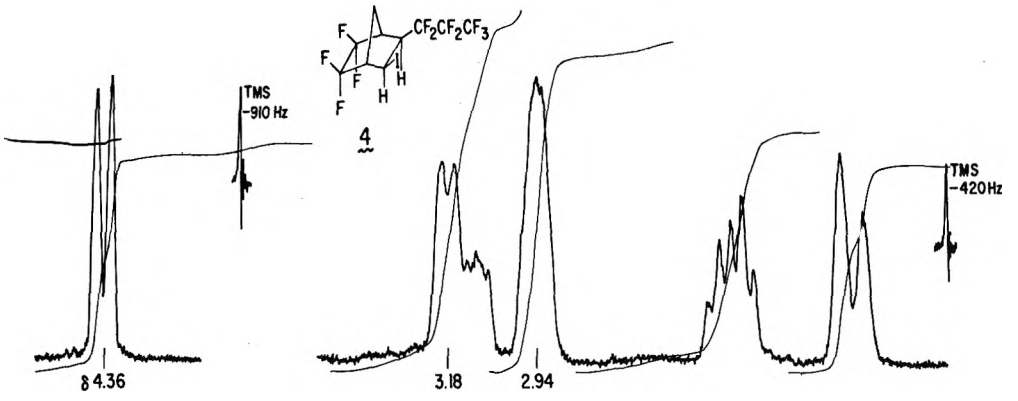


Figure 3.—Nmr (220 MHz) spectrum of *exo*-2-(*n*-heptafluoropropyl)-*exo*-3-iodo-5,5,6,6-tetrafluoronorbornane (4).

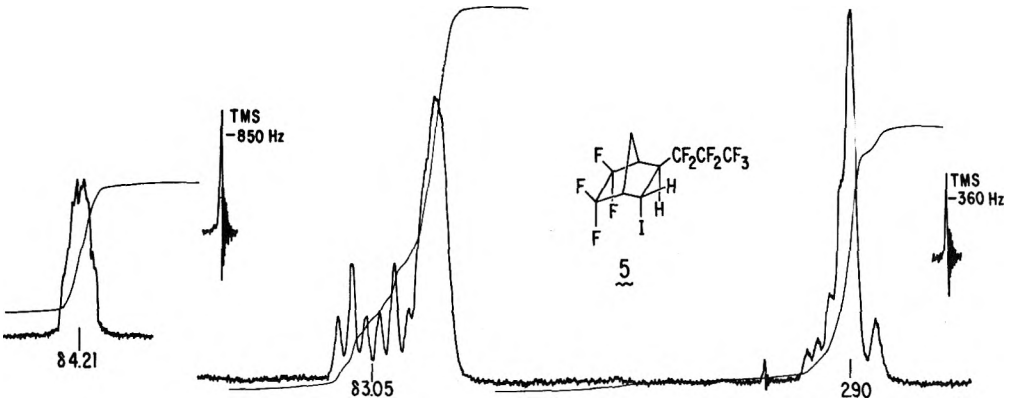


Figure 4.—Nmr (220 MHz) spectrum of *exo*-2-(*n*-heptafluoropropyl)-*endo*-3-iodo-5,5,6,6-tetrafluoronorbornane (5).

TABLE III

CHEMICAL SHIFTS[a] FOR CARBON TETRACHLORIDE ADDUCTS OF 5,5,6,6-TETRAFLUORO-2-NORBORNENE (1) AND NORBORNENE IN CARBON TETRACHLORIDE

Chemical shift	2a	6[b]	3a	7[b]
H_1	3.09	2.74	2.99[c]	2.6[d]
H_4	2.91	2.54		
H_{2n}	3.52	2.94	3.42	2.6[d]
H_{3n}	4.58	4.18		
H_{3x}			4.28	4.23
H_{7a}	2.04		1.98	1.38
H_{7s}	2.73	2.38	2.36	2.10

[a] See Table I, footnote *a*. [b] Values taken from ref 2a. [c] H_1, H_4 not resolved. [d] Not determined accurately owing to interferences.

(0.4–0.8 ppm) relative to the nonfluorinated adducts **6**, **7**. Note, however, that H_{3x} is not appreciably deshielded (0.05 ppm) from **2a** and **7**. Comparison of the methylene bridge protons indicates that H_{7a} is deshielded (0.6 ppm) from **3a** and **7**, whereas H_{7s} is deshielded less (0.26 ppm). These data suggest a *positive* magnetic anisotropy for the carbon–fluorine bond. Endo 5,6 fluorines deshield H_2, H_3 and exo 5,6 fluorines deshield H_{7a}. Fluorine substitution, however, does not affect H_{3x}, in agreement with a "through space" proximity effect. Introduction of endo 5,6 fluorines and the resultant deshielding of endo 2,3 protons, while not affecting the exo protons, thus has reversed the normal relative exo,endo proton shifts relationship for 2,3-halogenated norbornenes.[10]

(10) The ^{19}F spectra of the polyhalomethane adducts and related systems will be discussed in a future publication.

Discussion

Table IV summarizes the comparative additions of polyhalomethanes to norbornene and 5,5,6,6-tetrafluoro-2-norbornene (1). The predominance of trans addition with norbornene clearly is not the case for **1**. Cis addition is in fact preferred for carbon tetrachloride and bromotrichloromethane.

TABLE IV

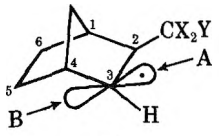
FREE-RADICAL ADDITION OF POLYHALOMETHANES TO 5,5,6,6-TETRAFLUORO-2-NORBORNENE (1) AND NORBORNENE

	Norbornene		Tetrafluoronorbornene (1)	
Adduct	% trans	% cis	% trans	% cis
CCl_3	95	5[a]	27	73
CCl_3Br	100	0[b]	32	68
n-C_3F_7I	100	0[c]	79	21

[a] Reference 2a. [b] Reference 2b. [c] Reference 3.

The overwhelming predominance of exo attack by trichloromethyl and *n*-heptafluoropropyl radicals has been noted previously by Osborne[2a] and Brace.[3] Subsequent transfer of halogen occurred primarily by path B, owing to major nonbonded interaction with the exo polyhalomethyl substituents, with resultant trans product formation. The initial addition of $\cdot CX_2Y$ should be independent of fluorine substitution at C_5 and C_6 and this was the case for **1**. The relative nonbonded repulsions between endo 5-fluorine and the 2-exo polyhalomethyl group with the approaching polyhalomethane molecule will then determine the preference for cis or trans product formation. The endo fluorine substituents are known to direct the stereo-

chemistry of free-radical attack by bromine.[1] The preference for cis addition of carbon tetrachloride and bromotrichloromethane to **1** also illustrates the importance of fluorine nonbonded interactions. Coulombic repulsion from the 5-endo fluorine toward the incoming polyhalomethane molecule is greater than the nonbonded interaction of the exo trichloromethyl group with polyhalomethane, and attack from side A in **8** is preferred with the result that predominantly cis



X = Y = Cl
X = F; Y = CF_2CF_3

8

adducts **2a** and **2b** are formed.[11] The slightly greater amount of trans addition observed with bromotrichloromethane reflects the increased importance of steric interaction of trichloromethyl with the larger polyhalomethane molecule.

The *n*-heptafluoropropyl group in **8** (X = F; Y = CF_2CF_3) is sterically large and rich in electron density. Attack from side A is subject to electronic repulsion from a number of fluorines of the large *n*-heptafluoropropyl group, while attack from B is repulsed by a single endo 5-fluorine substituent. The overall preference for trans addition reflects these factors. The fact that 21% cis addition is observed when none is observed for norbornene itself indicates that the endo fluorine substituents still play an important role in directing the stereochemistry of attack by *n*-heptafluoropropyl iodide.

Experimental Section

All melting and boiling points are uncorrected. The gas chromatography work was performed on a Varian Aerograph Series 200 gas chromatograph fitted with a Brown Potentiometer recorder. The following columns were employed: column A, 6 ft × 0.375 in. 20% QF-1 fluorosilicone on 60/80 Chromosorb P; column B, 6 ft × 0.375 in. 20% silicone 200 on 60/80 Chromosorb W; column C, 6 ft × 0.375 in. 20% Zonel E7 on 60/80 Chromosorb P. The ^1H and ^{19}F nmr spectra and decoupling experiments were run as before.[1]

(11) The formation of telomeric residues from the addition of polyhalomethanes to **1** reflects the importance of hindrance to chain transfer in **8**. For a discussion of this point, see ref 2a.

exo-2-Trichloromethyl-*exo*-3-chloro-5,5,6,6-tetrafluoronorbornane (**2a**) and *exo*-2-Trichloromethyl-*endo*-3-chloro-5,5,6,6-tetrafluoronorbornane (**3a**).—A mixture of 11.6 g (0.07 mol) of 5,5,6,6-tetrafluoro-2-norbornene (**1**), 77 g (0.5 mol) of carbon tetrachloride, and 1.2 g (5 mmol) of benzoyl peroxide was refluxed for 20 hr in a nitrogen atmosphere. A mixture of 84% **2a** and **3a** and 16% unreacted **1** was present by nmr. Vpc analysis (columns A and B, 165°) indicated a mixture of 73% **2a** and 27% **3a**. Removal of the solvent and fractionation afforded two major cuts, 9.9 g (97% **2a**, 3% **3a**), bp 64–54° (0.5 mm), and 3.7 g (10% **2a**, 90% **3a**), bp 68–69° (0.5 mm). A dark, viscous residue (5.7 g) remained. Preparative vpc (column A, 165°) gave pure **3a** as an oil, and pure **2a**, mp 36–38°.

Anal. Calcd for $C_8H_6Cl_4F_4$: C, 30.03; H, 1.89; Cl, 44.32. Found (**2a**): C, 30.30; H, 1.81; Cl, 44.42. Found (**3a**): C, 30.17; H, 1.96; Cl, 44.05.

A mixture of 0.5 g of 90% **3a** and 10% **2a**, 4 g of carbon tetrachloride, and 50 mg of benzoyl peroxide was refluxed for 4 hr under nitrogen. Vpc analysis indicated no change in the **3a**:**2a** ratio.

exo-2-Trichloromethyl-*exo*-3-bromo-5,5,6,6-tetrafluoronorbornane (**2b**) and *exo*-2-Trichloromethyl-*endo*-3-bromo-5,5,6,6-tetrafluoronorbornane (**3b**).—A mixture of 11.6 g (0.07 mol) of **1**, 99 g (0.5 mol) of bromotrichloromethane, and 1.2 g of benzoyl peroxide was refluxed for 24 hr in a nitrogen atmosphere to afford a mixture of 68% **2b** and 32% **3b** (vpc, column B, 175°). No unreacted **1** was present. Fractional distillation afforded the following cuts, bp 69–72° (0.3 mm): 3.5 g (99% **2b**, 1% **3b**), bp 72–73° (0.3 mm); 1.8 g (93% **2b**, 7% **3b**), bp 73–74° (0.3 mm); 13.2 g (74%, **2b**, 26% **3b**), bp 74–75° (0.3 mm); 2.9 g (15% **2b**, 85% **3b**). Treatment of the first cut with a small amount of pentane and chilling afforded pure **2b**, mp 42–44°. Pure **3b** was obtained as an oil by preparative vpc (column B, 175°).

Anal. Calcd for $C_8H_6BrCl_3F_4$: C, 26.37; H, 1.66; Br, 21.93; Cl, 29.19. Found (**2b**): C, 26.47; H, 1.69; Br, 22.14; Cl, 29.66. Found (**3b**): C, 26.45; H, 1.58; Br, 22.14; Cl, 29.67.

exo-2-(*n*-Heptafluoropropyl)-*exo*-3-iodo-5,5,6,6-tetrafluoronorbornane (**4**) and *exo*-2-(*n*-Heptafluoropropyl)-*endo*-3-iodo-5,5,6,6-tetrafluoronorbornane (**5**).—A 100-ml Carius tube charged with 8.3 g (0.05 mol) of **1**, 15 g (0.0507 mol) of freshly distilled *n*-heptafluoropropyl iodide, and 0.2 g of benzoyl peroxide was degassed and heated on a steam bath for 4.5 hr. Vpc (column C, 155°) and nmr analysis indicated 18% unreacted **1** and a mixture of 21% **4** and 79% **5**. Fractional distillation afforded 1.4 g of **1**, bp 48.5° (17 mm) (solidified), 2.2 g of 24% **4** and 76% **5**, bp 86–90° (17 mm): and 16.0 g of 19% **4** and 81% **5**, bp 90–100° (17 mm). Refractionation afforded the following mixtures, bp 86–93° (17 mm): 64% **4**, 36% **5**, bp 93–99° (17 mm); 41% **4**, 59% **5**, bp 99–100° (17 mm); 14% **4**, 86% **5**. Pure **5** was collected as a viscous, colorless oil by vpc (column C, 155°) and pure **4** was a white solid, mp 31–32°.

Anal. Calcd for $C_{10}H_6F_{11}I$: C, 26.00; H, 1.31; F, 45.23. Found (41% **4**, 59% **5**): C, 25.69; H, 1.28; F, 45.33.

Registry No.—**1**, 2822-56-2; **2a**, 39037-43-9; **2b**, 39037-44-0; **3a**, 39037-45-1; **3b**, 39037-46-2; **4**, 39037-47-3; **5**, 39037-48-4; CCl_4, 56-23-5; $CBrCl_3$, 75-62-7; *n*-heptafluoropropyl iodide, 754-34-7.

Fluorinated Bicyclics. III. Free-Radical Chlorination of 5,5,6,6-Tetrafluoro-2-norbornene

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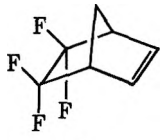
Free-radical chlorination of 5,5,6,6-tetrafluoro-2-norbornene (1) in carbon tetrachloride with a limited amount of molecular chlorine gave a mixture of cis (2a) and trans (3a) adducts in 3.2:1 ratio. Polychlorination occurred with excess chlorine to afford 2,2-dichloro-*exo*-3-chloro-5,5,6,6-tetrafluoronorbornane (4). The importance of endo 5,6-fluorine substitution in directing the stereochemistry of these reactions is discussed.

The free-radical bromination of 5,5,6,6-tetrafluoro-2-norbornene (1) was shown to proceed stereospecifically



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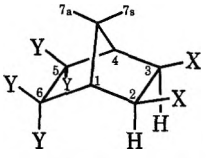
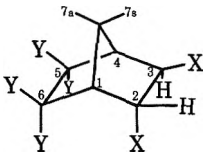


2a, X = Cl; Y = F
b, X = Br; Y = F
c, X = Cl; Y = H
d, X = Br; Y = H

to the cis-exo dibromide **2b**.[1] Poutsma demonstrated that free-radical chlorination of norbornene itself gave a 17:19 ratio of cis (**2c**) to trans (**3c**) dichloride products.[2] In light of these results, a comparative investigation of the free-radical chlorination of **1** and norbornene was undertaken to evaluate the effect of fluorine substitution.

Results

The fluorinated olefin **1** was inert to molecular chlorine in carbon tetrachloride solution at 25° in the dark. Upon irradiation with a 275-W sun lamp, the reaction was instantaneous. Treatment of **1** with 0.88 equiv of chlorine under these conditions afforded two products (>98%) in the ratio of 19:6 by vpc. Nmr analysis identified the cis adduct **2a** as the major product and **3a** as the minor product.



3a, X = Cl; Y = F
b, X = Br; Y = F
c, X = Cl; Y = H
d, X = Br; Y = H

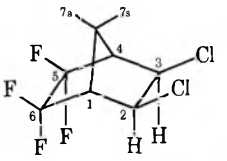
The 100-MHz spectra of **2a** and **3a** are displayed in Figures 1a and 1b. The chemical-shift and coupling-constant data are given in Tables I and II. Appropriate double-resonance experiments allowed for the assignment of long-range couplings.

The vicinal H_2, H_3 protons in **2a** gave a sharp doublet (J = 1.9 Hz) at δ 4.51. The methylene bridge proton

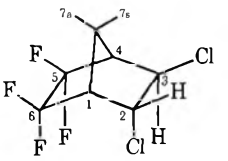
(1) B. E. Smart, *J. Org. Chem.*, **38**, 2027 (1973).
(2) M. L. Poutsma, *J. Amer. Chem. Soc.*, **87**, 4293 (1965).

TABLE I

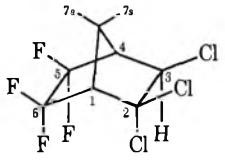
CHEMICAL SHIFTS[a] IN CARBON TETRACHLORIDE



2a



3a



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Nucleus	2a	3a	4
H_1, H_4	2.86	2.84	3.23, 2.81
H_2, H_3	4.51	4.23	..., 4.67
H_{7a}	1.98	2.05	2.11
H_{7s}	2.42	2.19	2.57
F_{5x}	118.9	118.7	119.9
F_{5n}	122.4	123.1	120.1
F_{6x}	118.9	110.5	108.5
F_{6n}	122.4	119.3	118.5

[a] All proton chemical shifts are in parts per million (δ) relative to internal tetramethylsilane. All fluorine chemical shifts are in parts per million (ϕ) relative to internal fluorotrichloromethane (F-11) internal standard. All values refer to the high-field side of F-11.

TABLE II

COUPLING CONSTANTS (HERTZ) IN CARBON TETRACHLORIDE

Nuclei	2a	3a	4
$H_{7s}H_{7a}$	12.5	12.5	13
H_3H_{7a}	1.9		2
$H_{7s}F_{6n}$	~5	~4	
$H_{7s}F_{6n}$	~5	3–4	5.8
$F_{5x}F_{5n}$	239	241	
$F_{6x}F_{6n}$	239	244	244

H_{7a} was the source of this splitting. The ^{19}F nmr spectrum of **2a** displayed a single AB quartet (J = 239 Hz), which suggests a symmetrical structure with the exo fluorines equivalent and the endo fluorines equivalent. Structure **2a** is consistent with these data. *exo-cis*-2,3-Dibromo-5,5,6,6-tetrafluoronorbornane[1] (**2b**) and **2a** gave very similar spectra.

The nmr structure proof for **3a** was less straightforward. Both H_2 and H_3 appeared as a multiplet at δ 4.23. This multiplet was not further resolved at 220 MHz. The ^{19}F nmr spectrum displayed a *pair* of AB quartets for the geminal fluorines, which suggests structure **3a**. The presence of an AB quartet of multiplets for H_{7a}, H_{7s} with long-range $F_{5n}H_{7s}$ and

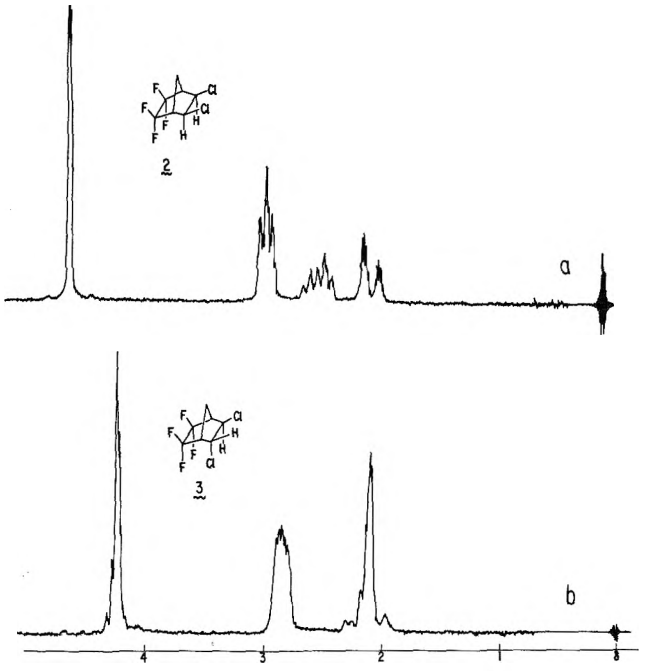


Figure 1.—Nmr (100 MHz) spectrum: a, *exo-cis*-2,3-dichloro-5,5,6,6-tetrafluoronorbornane (**2a**); b, *endo*-2-chloro-*exo*-3-chloro-5,5,6,6-tetrafluoronorbornane (**3a**).

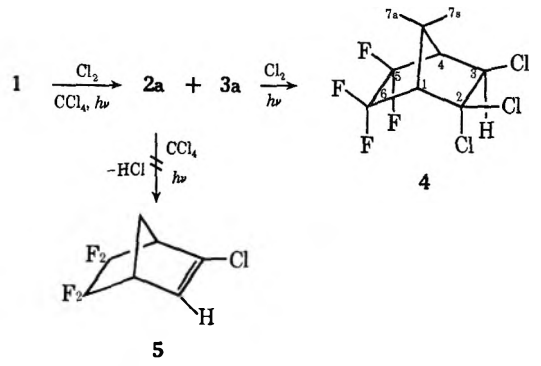
$F_{6n}H_{7s}$ couplings rules out an unprecedented rearranged 2,7-dichloride structure.

The equivalence of H_2 and H_3 in **3a** can be explained as follows. Comparison of the chemical shifts of the protons adjacent to chlorine in the cis (**2c**) and trans (**3c**) adducts with **2a** establishes the following shielding effects. Protons H_{2n} and H_{3n} in **2c** appear at δ 3.94[3] and fluorine substitution (**2a**) deshields H_n by 0.57 ppm (δ 4.51–3.94). With the assumption that 5,6-fluorine substitution does not appreciably affect the chemical shift of H_{2x},[4] H_{2x} in **3a** should appear at *ca.* δ 4.23, which is the value for H_{2x} in **3c**.[5] However, H_{3n} (δ 3.67)[5] in **3c** will be deshielded by the calculated value of 0.57 ppm upon fluorine substitution at C_5. Therefore, H_{3n} in **3a** should appear at *ca.* δ 3.67 + 0.57 = 4.24, which is equivalent to the chemical shift of H_{2x}. Both H_{2x} and H_{2n} are indeed observed at δ 4.23 in **3c**, which is in excellent agreement with these calculations.

The radical chlorination of **1** with 2.5 equiv of chlorine gave a quantitative yield of two products. The major product (97%) was assigned structure **4** and the minor product (3%) was *exo*-2-trichloromethyl-*exo*-3-chloro-5,5,6,6-tetrafluoronorbornane.[4]

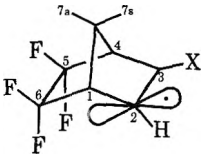
The 100-MHz nmr spectrum of **4** displayed a narrow multiplet ($W_{1/2}$ = 4 cps) for a single proton adjacent to chlorine at δ 4.67 (Table I). Decoupling experiments established that this proton was not coupled to H_4 with the expected value of ~4 Hz for an exo proton. Coupling of *ca.* 2 Hz with the methylene bridge proton H_{7a} was present. The source of additional fine couplings (<0.5 Hz) was not established.

Solutions of pure **2a** and pure **3a** were irradiated under the reaction conditions in the absence of chlorine. No isomerization occurred and elimination of HCl was not observed. Polychlorination therefore proceeds by direct attack on **2a** and **3a**, without the intermediacy of olefin **5**.



Discussion

The preference for cis-exo-chlorination of 5,5,6,6-tetrafluoro-2-norbornene relative to norbornene is consistent with the previously observed stereochemical control by fluorine substitution.[1,4] Potential severe coulombic repulsion between the propagating chlorine molecule and an endo fluorine in intermediate **6a** results in a preference for exo attack.



6a, X = Cl
b, X = Br

The difference in stereospecificity of bromination and chlorination of **1** is noteworthy. While bromination is exclusively cis-exo,[1] a significant amount of trans product (24%) is formed on chlorination. In comparison of attack of halogen on **6a** and **6b**, it is reasonable to predict a preference for exo attack by chlorine on **6a** relative to exo bromine attack on **6b**, since Br–Br interaction is more severe than Cl–Cl interaction. The relative amount of radical cis chlorination *vs.* bromination of norbornene itself supports this contention.[1,2] However, the opposite is predicted for endo attack, where F–Br nonbonded repulsion is more severe than F–Cl repulsion assuming similar pathways of attack on **6**. The observed preference for cis attack on bromination relative to chlorination suggests that the difference between F–Br and Br–Br nonbonded interactions is greater than between F–Cl and Cl–Cl interactions.

A semiquantitative approach to this problem can be given as follows. As a first approximation, assume that the transition state for halogenation occurs very late along the reaction coordinate with considerable bond making present. The geometry of the transition state will then be very similar to that of the product. The appropriate transition-state geometries can be expressed in cartesian coordinates with the further assumption that no changes in bond angles or bond lengths from norbornane itself exist (Appendix A). The van der Waals interactions of the propagating halogen species and the norbornane substituents in the transition state can then be approximated by the halogen atom substituent interactions in the product.

(3) Value taken from D. D. Tanner and G. C. Gidley, *J. Org. Chem.*, **33**, 38 (1968).
(4) B. E. Smart, *J. Org. Chem.*, **38**, 2035 (1973).
(5) Values taken from ref 2.

For example, exo attack of bromine on **6b** will result in the nonbonded interactions Br_{2x}–Br_{3x}, H_{7s}–Br_{2x}, F_{6n}–H_{2n}, and H_{2n}–H_{3n}. The magnitude of these individual interactions can be calculated from the Hill equation[6] and the sum of such interactions will represent the approximate net coulombic interaction in a late transition state. The results are given in Tables III and IV.

TABLE III
VAN DER WAALS INTERACTIONS

Nonbonded interaction	Distance, Å	E_V, kcal/mol
H_7Cl_{2x}	3.018	−0.13
H_7H_{2x}	2.772	−0.03
H_7Br_{2x}	3.007	−0.15
$H_{2x}Cl_{3x}$	2.618	0.08
$H_{2x}Br_{3x}$	2.707	0.20
$H_{6n}Cl_{2n}$	2.291	1.64
$H_{6n}Br_{2n}$	2.329	3.01
$F_{6n}Cl_{2n}$	2.198	8.01
$F_{6n}Br_{2n}$	2.219	14.09
$Br_{2x}Br_{3x}$	2.872	10.11
$Cl_{2x}Cl_{3x}$	2.732	4.91
$H_{2n}H_{3n}$	2.304	−0.05
$H_{2n}H_{6n}$	2.246	−0.04
$H_{2n}F_{6n}$	2.557	−0.08

TABLE IV
SUMMATION OF VAN DER WAALS INTERACTIONS

Product	Nonbonded interactions	ΣE_V, kcal/mol
2a	$H_{2n}F_{6n}$, $H_{2n}H_{3n}$, $H_{7s}Cl_{2x}$, $Cl_{2x}Cl_{3x}$	4.65
2b	$H_{2n}F_{6n}$, $H_{2n}H_{3n}$, $H_{7s}Br_{2x}$, $Br_{2x}Br_{3x}$	9.84
2c	$H_{6n}H_{2n}$, $H_{2n}H_{3n}$, $H_{7s}Cl_{2x}$, $Cl_{2x}Cl_{3x}$	4.70
2d	$H_{6n}H_{2n}$, $H_{2n}H_{3n}$, $H_{7s}Br_{2x}$, $Br_{2x}Br_{3x}$	9.88
3a	$H_{7s}H_{2x}$, $H_{2x}Cl_{3x}$, $H_{3n}Cl_{2n}$, $F_{6n}Cl_{2n}$	8.14
3b	$H_{7s}H_{2x}$, $H_{2x}Br_{3x}$, $H_{3n}Br_{2n}$, $F_{6n}Br_{2n}$	14.46
3c	$H_{7s}H_{2x}$, $H_{2x}Cl_{3x}$, $H_{3n}Cl_{2n}$, $H_{6n}Cl_{2n}$	1.77
3d	$H_{7s}H_{2x}$, $H_{2x}Br_{3x}$, $H_{3n}Br_{2n}$, $H_{6n}Br_{2n}$	3.38

These calculations clearly reflect the preference for trans product formation from norbornene and cis product from **1**. A net coulombic repulsion of 9.88 kcal is observed for the formation of **2d**, while 3.38-kcal repulsion is observed for **3d**. In the fluorinated case, exo attack by bromine results in 9.84-kcal repulsion whereas endo attack nets 14.46-kcal repulsion. The preference for cis-exo product formation in bromination of **1** is correctly predicted. The same trend is evident for chlorination. It should be emphasized that the absolute values obtained from the Hill equation are subject to error owing to uncertainty in the parameters employed, although the differences in net coulombic interactions are meaningful.

A second approximation which includes dipole–dipole interactions also can be made. If the assumption of a late transition state is retained, the net dipole–dipole interaction can be calculated as a sum of the individual C–X (X = Br, Cl, F) dipole interactions. The dipoles were taken as vectors along the C–X bond axis in the case of X = Br, Cl and the same norbornane skeletal geometry described above was employed. The C–F dipole was taken as a vector sum of the $C–F_{6n}$ and $C–F_{6x}$ dipoles with a net charge separation of 0.4 eu.[7] Since the cartesian coordinates of each atom are already assigned, the net dipole–dipole interaction can most easily be calculated as the sum of the coulombic charge–charge interactions assuming 0.19- and 0.22-eu charge separation for the C–Br and C–Cl bonds, respectively.[7,8] Table V summarizes the results.

TABLE V
DIPOLE–DIPOLE INTERACTIONS

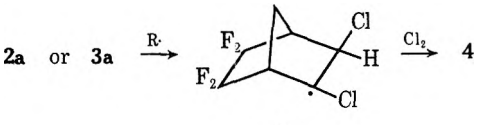
Product	ΣE_D, kcal/mol
2a	4.12
3a	1.21
2b	3.91
3b	1.70
2c	0.48
3c	−1.40
2d	0.55
3d	−0.81

For the chlorination and bromination of **1** the dipole–dipole and van der Waals interaction sum ($E_V + E_D$) gives 8.77 kcal for **2a**, 9.35 kcal for **3a**, 13.75 kcal for **2b**, and 16.16 kcal for **3b**. If entropy effects are neglected, these values predict 94% cis-exo-bromination ($\Delta\Delta G^{\ddagger}$ = 2.41 kcal) and 73% cis-exo-chlorination ($\Delta\Delta G^{\ddagger}$ = 0.58 kcal). These values are in excellent agreement with the experimental results.

An approximation of the coulombic interactions involved in an early transition state model was also attempted (Appendix B). Attack of halogen at C_2 perpendicular to the C_1–C_2–C_3 plane with C–X distances twice that of the normal carbon–halogen bond distance was examined. This model indicates that only interaction with the 6-endo substituent is important, and exclusively cis-exo halogenation is predicted for both **1** and norbornene. The magnitude of the endo-fluorine halogen interaction (65–98 kcal) is also suspect. This model is at variance with the experimental results and was not further examined.

Polychlorination of **1** involves the initial formation of **2a** and **3a** followed by subsequent radical chlorination.

Hydrogen abstraction from **2a** necessarily affords intermediate radical **7**. Preferential exo hydrogen



7

abstraction from **3a** is anticipated since the endo 3-hydrogen is shielded from attack by both endo 5-fluorine and endo 2-chlorine substituents. Hence, both **2a** and **3a** give the same intermediate radical **7** and subsequent chlorine attack (either exo or endo) affords **4**.

Experimental Section

All melting and boiling points are uncorrected. The gas chromatography work was performed as before[1] with a 6 ft × 0.375 in. 20% QF-1 fluorosilicone on 60/80 Chromosorb P column. The ^1H and ^{19}F nmr spectra and decoupling experiments were run as before.[1]

(6) T. L. Hill, *J. Chem. Phys.*, **16**, 399 (1948).

(7) W. A. Sheppard, "Organic Fluorine Chemistry," W. A. Benjamin, New York, N. Y., 1969, pp 19–21, and references cited therein.

(8) Calculation of dipole–dipole interactions by the procedure of Lehn and Ourisson gave comparable results; see J.-M. Lehn and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1113 (1963).

exo-cis-2,3-Dichloro-5,5,6,6-tetrafluoronorbornane (2a) and *endo*-2-Chloro-*exo*-3-chloro-5,5,6,6-tetrafluoronorbornane (3a).—A solution of 8.3 g (0.05 mol) of 1 in 75 ml of carbon tetrachloride in a nitrogen atmosphere was treated with 3.1 g (0.044 mol) of chlorine and irradiated with a 275-W sun lamp at *ca.* 6 in. from the reaction vessel. Uptake was rapid, as evidenced by the disappearance of the yellow-green color. Irradiation was discontinued 5 min after complete addition of chlorine and the carbon tetrachloride solvent was removed by flash distillation. Nmr of the crude product indicated a mixture of 26% unreacted 1 and 74% (2a + 3a). Vpc analysis (150°) gave 1 (25%) at 1.65 min, 2a (57%) at 6.6 min, and 3a (18%) at 8.8 min. Preparative vpc with collection in a −78° trap gave 1.91 g of 1, 6.52 g of pure 2a, mp 52–53°, and 1.54 g of 3a, mp 25.5–26°.

Anal. Calcd for $C_7H_6Cl_2F_4$: C, 35.47; H, 2.55; Cl, 29.92. Found (2a): C, 35.48; H, 2.67; Cl, 29.78. Found (3a): C, 35.20; H, 2.73; Cl, 29.72.

Samples of pure 2a and 3a in carbon tetrachloride (0.1 g/4 ml) were individually irradiated for 30 min with a 275-W sun lamp. The isomers remained unchanged by vpc and nmr.

2,2-Dichloro-*exo*-3-chloro-5,5,6,6-tetrafluoronorbornene (4).—A solution of 5.8 g (0.035 mol) of 1 in 75 ml of carbon tetrachloride was treated with 4.2 g (0.087 mol) of chlorine as above. Irradiation was continued for 30 min after chlorine addition, and removal of excess chlorine and solvent afforded a mixture of 97% 4 and 3% *exo*-2-trichloromethyl-*exo*-3-chloro-5,5,6,6-tetrafluoronorbornane by vpc (175°). The latter compound was identified by coinjection and identical retention time with an authentic sample.[4] Fractionation afforded 7.1 g of pure 4 as a ceraceous, bad-smelling solid, bp 72–73° (0.7 mm), mp 56–59°. A pot residue (1.2 g) of 83% 4 and 17% carbon tetrachloride adduct along with three unidentified minor products (<10%) remained.

Anal. Calcd for $C_7H_3Cl_3F_4$: C, 30.97; H, 1.86; Cl, 39.18. Found: C, 30.97; H, 1.76; Cl, 39.00.

A similar reaction with 1.0 g (6 mmol) of 1 in 50 ml of methylene dichloride with 6.2 g (87 mmol) of chlorine afforded 100% 4.

Registry No.—1, 2822-56-2; 2a, 39037-49-5; 2b, 39037-29-1; 2c, 14627-75-9; 2d, 2843-50-7; 3a, 39037-53-1; 3b, 39037-54-2; 3c, 2843-43-8; 3d, 2843-42-7; 4, 39037-57-5.

Acknowledgments.—Dr. Derick Ovenall and Mr. Lou Walther are acknowledged for their assistance in obtaining the nmr spectra. Dr. H. E. Simmons is also acknowledged for his many helpful suggestions.

Appendix A. Geometries and van der Waals Interactions

The cartesian coordinates (Table VI) were derived from the published values for norbornane.[9] The following bond distances were employed: C–H, 1.12 Å; C–Cl, 1.78 Å; C–Br, 1.93 Å; C–F, 1.38 Å. The heteroatom coordinates were determined by extending the C–H vector of length 1.12 Å to a new C–X vector with the appropriate C–X bond length. Otherwise the reported C, H coordinates for norbornane were used.

TABLE VI

H_{2x} (0, −0.902, 1.699)	Cl_{2x} (1.384, 1.063, −2.577)
H_{2n} (1.152, −2.184, −0.472)	Cl_{2n} (1.384, −1.063, −2.577)
H_{6n} (1.152, −1.123, −1.931)	Cl_{6n} (1.384, −2.780, −0.216)
H_{7s} (1.152, 1.123, −1.931)	F_{6x} (1.248, 2.430, −0.366)
Br_{2x} (1.436, −2.912, −0.159)	F_{6n} (1.248, 1.098, −2.197)
Br_{2n} (1.436, −1.050, −2.720)	

(9) J. F. Chiang, C. F. Wilcox, Jr., and S. H. Bauer, *J. Amer. Chem. Soc.*, **90**, 3149 (1968).

The nonbonded coulombic atom–atom interactions were calculated from the Hill equation (eq 1). The published nonbonded constants were employed.[6,10]

$$E_V/\epsilon = -2.26\alpha^{-6} + 8.28\cdot 10^5 e^{-\alpha/0.0736} \quad (1)$$

Appendix B. Early Transition-State Geometries and van der Waals Interactions

The C, H, and heteroatoms at C_6 and C_{3x} were defined by the above coordinates and the published coordinates for norbornane. Atom C_2 (0.776, −1.220, −0.886) was transposed to (0, 0, 0) and the cross products C_1–C_2 × C_2–C_3 and C_2–C_3 × C_1–C_2 defined the axis of exo and endo attack at C_2 perpendicular to the C_1–C_2–C_3 plane. The C_2–X distance was chosen and the coordinates for the heteroatom X (Table VII) were determined by the ratio of the cross product length and the C_2–X length. Transposition of this new vector C_2–X to C_2 (0.776, −1.220, −0.886) finally assigned the coordinates of X in this model. The appropriate nonbonded interactions (Table VIII) were calculated from the Hill equation.

TABLE VII

C–X	Å	Coordinates	
		Br_{2x}	Br_{2n}
X = Br	3.86	(0.776, −3.444, 2.238)	(0.776, 1.004, −4.010)
X = Br	5.76	(0.776, −4.556, 3.800)	(0.776, −2.116, −5.572)
		Cl_{2x}	Cl_{2n}
X = Cl	3.56	(0.776, −3.272, 1.996)	(0.776, 0.832, −3.768)
X = Cl	5.34	(0.776, −4.298, 3.437)	(0.776, 1.858, −5.209)

TABLE VIII

Interaction	Distance, Å[a]	E_V,[a] kcal/mol
H_7Br_{2x}	2.712, 4.286	0.18, −0.05
$H_{6n}Br_{2n}$	2.116, 3.793	8.83, −0.09
$H_{3n}Br_{2n}$	3.545, 5.241	−0.12, −0.01
H_7Cl_{2x}	2.511, 3.885	0.34, −0.05
$H_{6n}Cl_{2n}$	1.897, 3.380	13.84, −0.10
$H_{3n}Cl_{2n}$	3.304, 4.832	−0.12, −0.02
$F_{6n}Cl_{2n}$	1.662, 3.142	97.75, −0.22
$F_{6n}Br_{2n}$	1.876, 3.557	65.13, −0.23
$Cl_{2x}Cl_{3x}$	3.130, 4.507	0.29, −0.17
$Br_{2x}Br_{3x}$	3.305, 4.824	0.95, −0.25

[a] First entry corresponds to C–X transition state of length twice normal C–X bond distance and the second entry to a length three times the normal bond length.

(10) E. Eliel, *et al.*, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 449–453.

Directive Influence of the Keto Bridge on the Isomerization Pathways of 2,3-Dicarbonyl-2,3-diazanorbornen-7-one Derivatives

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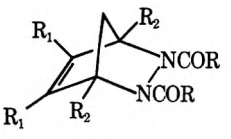
The keto bridge in the adducts **5** of 2,5-dimethyl-3,4-diphenylcyclopentadienone with azo esters profoundly increases the lability of the adducts toward clean thermal isomerization. A reversible [3,3] sigmatropic rearrangement to the 1,3,4-oxadiazine derivatives **6** is observed, along with a slower, and perhaps irreversible, [1,3] sigmatropic rearrangement to the diazetidines **7**, the stable thermal end products. Both the isomerizations of **5** to **6** and **5** to **7** can be reversed by photolysis, which also causes decarbonylation of **5** to the 1,2-dihydropyridazine esters **10**. Reaction of the cyclone with azodiacyls leads to the quantitative isolation of the oxadiazines **16**, but the intermediacy of the initial Diels–Alder adduct **15** could be shown by nmr spectroscopy.

We have recently shown[1,2] that the adducts **1** from azodiacyls and cyclopentadiene undergo a [3,3] sigmatropic rearrangement to the racemic oxadiazines **2**



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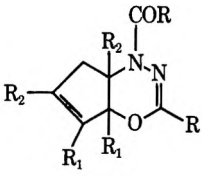

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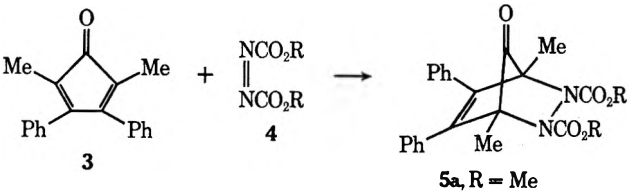


3 **4** **5a**, R = Me; **b**, R = Et; **c**, R = CH_2CCl_3; **d**, R = Ph; **e**, R = CMe_3

(one enantiomer from each of two pathways) under circumstances which indicated that the reaction was concerted. Accelerating effects were noted by increasing the bulk of R in the amide group,[2] and by the presence of vinyl (R_1) and bridgehead (R_2) substituents.[1] Replacement of the amide by urethane groups (R = acyloxy), however, completely inhibited the rearrangement.[3]

We now wish to report that a keto bridge lowers remarkably the thermal stability of the diazanorbornene system in the adducts of both azodiacyls and azo esters, and that, in particular, in the case of the adducts **5** of azo esters with 2,5-dimethyl-3,4-diphenylcyclopentadienone a delicately balanced set of competing isomerizations is observed.

Results

The reaction of the cyclone **3** (as its dimer) with the azo esters **4** was conveniently followed in refluxing carbon tetrachloride by nmr spectroscopy, which showed the buld-up of the *tert*-methyl singlet in the adducts **5**. In the late stages additional methyl singlets began to appear before reaction of **3** and **4** was complete. The optimum reflux times for each azo ester (yields of at least 90%) are shown in Table I and point out their wide variation in reactivity. The adducts **5a** and **5d** were crystalline and the others were glassy solids; spectroscopic properties of interest are also listed in Table I.

The peaks developing in the nmr spectrum during the late stages of the azo ester reactions were again observed when solutions of the pure adducts **5** were refluxed, slowly in carbon tetrachloride, more rapidly in tetrachloroethylene. Specifically, a solution of **5a** showed eight new methyl peaks in its spectrum in tetrachloroethylene, four of which reached a maximum and then decreased, while the others continued to grow and finally (about 4 days) accounted for the total methyl absorption.

Repetition on a large scale and work-up gave a nearly quantitative yield of an isomer of **5a**, mp 200–201°; the same compound could be obtained more readily by refluxing either **5a** or equimolar amounts of **3** and and **4a** in bromobenzene for 5 hr. The uv absorption of the isomer at 284 nm (ϵ 13,000) was indicative of the conjugated α-methyl-β-phenyl cyclopentenone chromophore,[5] but the ir bands at 1768, 1740, and 1722 cm^{-1}, and the absence of absorption between 1720 and 1620 cm^{-1}, allowed confident rejection of the expected 1,3,4-oxadiazine structure **6a**. Absorption for C=N in the region 1680–1660 cm^{-1} has been well established for a number of oxadiazines derived from azo esters.[6]

While the uv and ir spectra were consistent with those predicted for the diazetidine **7a**, two features, in its nmr and its mass spectra, were not easily reconciled with the formulation **7a**. The nmr spectrum (CCl_4) had methyl peaks at τ 8.87, 7.90, 7.05, and 6.22, of which the first two and the last could be readily assigned to a *tert*-methyl, a vinyl methyl, and an ester methyl, respectively. The peak at τ 7.05, however, was at an unusually high field for any methoxy group. Furthermore, the high-resolution mass spectrum con-

(1) D. Mackay, J. A. Campbell, and C. P. R. Jennison, *Can. J. Chem.*, **48**, 81 (1970).

(2) J. A. Campbell, D. Mackay, and T. D. Sauer, *Can. J. Chem.*, **50**, 371 (1972).

(3) The adducts of dimethyl azodicarboxylate with cyclopentadiene and with 1,4-dimethyl-2,3-diphenylcyclopentadiene decompose slowly on heating at about 230 and 150°, respectively, but the reactions are complex. In each case several volatile products (gc) and colored high molecular weight material are formed; the total ir spectrum shows strong NH absorption.[4]

(4) D. Mackay, C. W. Pilger, and L. Wong, unpublished observations.

(5) C. F. H. Allen, T. Davis, D. W. Stewart, and J. A. VanAllan, *J. Org Chem.*, **20**, 310 (1955).

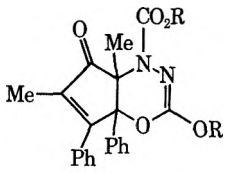
(6) J. Firl and S. Sommer, *Tetrahedron Lett.*, 1925, 1929 (1970); E. K. von Gustorf, D. V. White, B. Kim, D. Hess, and J. Leitich, *J. Org. Chem.*, **35**, 1155 (1970).

TABLE I

PREPARATION AND PROPERTIES OF ADDUCTS 5

Compd	Optimum time, hr	Mp, °C	ν (CCl_4),[a] cm^{-1}	τ (CCl_4) Pt[b]	τ (CCl_4) Ester	τ (CCl_4) C-Me
5a	24	119–120	1800, 1722, 1724	2.6–3.2	6.40 (Me)	8.20
5b	24	Glass	1800, 1744, 1718	2.6–3.2	5.90 (q, CH_2, J = 7.5 Hz) 8.97 (t, Me)	8.18
5c	2	Glass	1800, 1760, 1736	2.6–3.2	5.38 (AB q, CH_2, J = 12 Hz)	8.15
5d	1.5	Glass	1800, 1755, 1735	2.5–3.3	2.80 (Ph)[c]	8.05
5e	240	160–162	1800, 1732, 1716	2.6–3.2	8.65 (CMe_3)	8.26

[a] The 1800-cm^{-1} band is that of the bridging carbonyl. [b] Outer limits of absorption. [c] The sharp phenoxy peak dominates the broad phenyl pattern common to all the other adducts.



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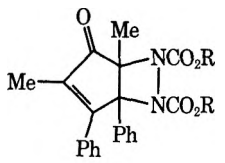

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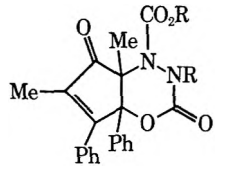

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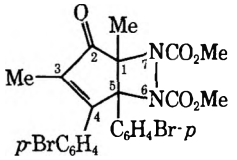


9

a, R = Me
b, R = Et
c, R = CH_2CCl_3
d, R = Ph
e, R = CMe_3

tained an intense peak (48% of the base peak) at m/e 275.1546 due to the oxygen-free ion $C_{19}H_{19}N_2^+$ which contained both nitrogen atoms and one methyl group from the original azo ester. Its occurrence was explicable only on the basis of a migration of methyl from oxygen to nitrogen or carbon during either the original isomerization of **5a** or the fragmentation of the product.

Both these spectroscopic observations were supportive of the presence of an *N*-methyl group in the isomer, a plausible structure being the 1,3,4-oxadiazin-2-one **8a**, which also fits the uv and ir data, and has credibility as the consequence of the expected[1,2] rearrangement of **5a** to **6a** (a hetero-Cope reaction), followed by a rapid [1,3] rearrangement of **6a** to **8a** (a modification of the Chapman[7] or the Chichibabin[8] rearrangement).

A decision between **7a** and **8a** was finally made on the basis of the X-ray analysis of the *p,p'*-dibromo analog. The synthesis of the latter involved the standard sequence[9,10] from *p,p'*-dibromobenzil to the dibromo derivative of the cyclone **3** (dimer, mp 180–182.5°), which was condensed with dimethyl azodicarboxylate to the dibromo derivative of **5a**. Isomerization in refluxing bromobenzene gave a product, mp 198.5–199.5°, whose spectra resembled those of the isomer of **5a** in all respects, including in particular a methyl absorption at τ 6.90 in its nmr and an abundant ion at m/e 432.9728 ($C_{19}H_{17}{}^{79}Br^{81}BrN_2^+$,) in its mass spectrum. X-Ray crystallography[11] showed this compound in fact to be the diazetidine **9**. Thus the stable end products of the isomerization of **5** are not the diazinones **8** but the diazetidines **7**.

In the crystal of **9** the methyl of the ester group on N-6 (see numbering scheme) is very close (*ca.* 3.4 Å) to the face of the phenyl ring on C-4.[11] If the assumption is made that the low-energy conformations in solution also have this ester group in a similar environment, the highly shielded absorption at τ 6.90 in **9** can be assigned to this methyl group.

The ion $C_{19}H_{19}N_2^+$ in the mass spectrum of **7a** has now recently been shown[4] to arise in a step involving decarboxylative migration of methyl from oxygen to nitrogen, and is an example of a general process in the fragmentation of cyclic bisurethanes, which may be formulated as $>NNCO_2R^+ \rightarrow RNN<^+ + CO_2$.

The diethyl adduct **5b** also gave a quantitative yield of the diazetidine **7b** on extended refluxing in tetrachloroethylene. The ditrichloroethyl adduct **5c**, however, gave an approximately equimolar yield of the diazetidine **7c** and the 1,2-dihydropyridazine ester **10c**, the product of decarbonylation; these were separated by fractional crystallization. The diphenyl adduct **5d** gave mainly the diazetidine **7d**, but a 10–15% yield of dihyropyridazine **10d** was evident in the nmr spectrum at the end of the reaction, though it was not isolated. The di-*tert*-butyl adduct **5e** gave only complex, tarry products on heating, among which neither **7e** nor **10e** could be positively identified. It appears that with the adducts derived from the azo esters of fairly acidic hydroxy compounds decarbonylation can compete with isomerization, but that bulky ester groups may inhibit both reactions.

The properties of the diazetidines **7a–d**, all of which were high-melting solids, are listed in Table II. The strong shielding of the ester group noted in **7a** and **9** takes an interesting form for the methylene group in **7b** and **7c**. Only one of the methylene protons is highly shielded in each case, and the resulting chemical shift differences in the pair, 0.92 ppm for **7b** and especially 1.98 ppm for **7c**, are remarkably large for geminal protons which are not part of a cyclic system. The simplest interpretation of this is that rotation of the methylene group is completely inhibited on the nmr time scale and that only one of the pair of protons is close to the face of the phenyl ring.[12]

(7) J. W. Schulenberg and S. Archer, *Org. React.*, **14**, 1 (1965); A. F. Hegarty, J. A. Kearney, M. P. Cashman, and F. L. Scott, *Chem. Commun.*, 689 (1971).

(8) R. A. Scherer and H. R. Beatty, *J. Org. Chem.*, **37**, 1681 (1972).

(9) F. R. Japp and J. D. Lander, *J. Chem. Soc.*, 123 (1897); F. R. Japp and J. Knox, *ibid.*, 673 (1905).

(10) F. W. Gray, *J. Chem. Soc.*, 2132 (1909).

(11) P. C. Chieh, D. Mackay, and L. Wong, *J. Chem. Soc., Perkin Trans. 2*, 2094 (1972).

(12) The line widths of the upfield protons are dependent on the field strength. This will be the subject of a forthcoming publication.

TABLE II

PREPARATION AND PROPERTIES OF DIAZETIDINES 7

Compd	Mp,[a] °C	ν (CCl4),[b] cm⁻¹	λmax (EtOH), nm (ε)	τ (CCl4) Ph[c]	τ (CCl4) Ester	τ (CCl4) Vinyl Me	τ (CCl4) tert-Me
7a	200–201	1768, 1740 1722	284 (13,000)	2.5–3.2	6.22 (Me), 7.05 (Me)	7.90	8.87
7b	178–179.5	1760, 1734 1720	282 (12,900)	2.5–3.2	5.73 (q, CH_2, J = 7.5 Hz), 6.10 (oct, H_A, AMX_3, J_{AX} = 7.5, J_{AM} = 10 Hz), 7.02 (oct, H_M), 8.70 (t, X_3, Me), 9.23 (t, Me)	7.93	8.83
7c	209–211	1778, 1750 1728	283 (13,300)	2.3–3.1	5.16 (AB q, CH_2, J = 12 Hz), 5.22 (d, H_A, AX, J_{AX} = 12 Hz), 7.20 (d, H_X)	7.88	8.69
7d	199–200	1778, 1750 1722	283 (13,500)	2.3–3.6		7.83	8.63

[a] 7a, 7b, and 7d from methanol, 7c from methanol–methylene chloride. [b] The first two peaks are due to the ester carbonyls, the third to the enone carbonyl. [c] Outer limits of absorption.

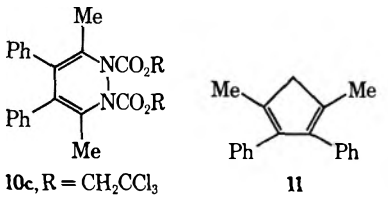
TABLE III

PREPARATION AND PROPERTIES OF OXIDIAZINES 6

Compd	Time,[a] hr	Yield,[a] %	Mp, °C	ν (CCl4),[b] cm⁻¹	λmax (MeOH), nm (ε)	τ (CCl4) Ph[d]	τ (CCl4) Ester and alkoxy[e]	τ (CCl4) Vinyl Me	τ (CCl4) tert-Me
6a	55	60	151–152	1741, 1699 1675	282 (13,000)	2.5–3.0	6.15 (s, Me), 6.22 (s, Me)	7.75	9.05
6b	96	55	Glass	1745, 1700 1670	281 c	2.5–3.0	5.79 (q, CH_2), 5.87 (q, CH_2), 8.70 (t, 2 Me, J = 7.5 Hz)	7.85	9.06
6c	30	60	Glass	1748, 1715 1680	280 (13,600)	2.5–3.0	5.38 (broad s, 2 CH_2)	7.84	8.93
6d	24	60	161–162	1745, 1700 1685	284 (12,900)	2.5–3.1		7.78	8.82

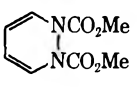
[a] Optimum values, determined by nmr analysis during the reaction. [b] Peaks in order: ester C=O, enone C=O, C=N. [c] Intensity not determined. [d] Outer limits of absorption. [e] Not possible to say which is which. In $CDCl_3$ the methoxy peaks of 6a are coincident.

The identities of the decarbonylation products **10c** and **10d** followed from their symmetrical nmr absorption pattern (methyl singlet near τ 7.8) and, for **10c**, the uv bands at 245 (ϵ 17,300) and 270–300 nm (broad shoulder, ϵ 4000 at 295 nm). Each of these bands is found separately in the model compounds, the diene **11** (240 nm, ϵ 18,000)[13] and the simple dihydropyridazine **12** (296 nm, ϵ 2900).[14] Their presence together is a powerful argument for structure **10** and precludes the alternative symmetrical 2,3-diazabicyclo[2.2.0] derivative **13**, whose chromophore would resemble



10c, R = CH_2CCl_3
d, R = Ph

11



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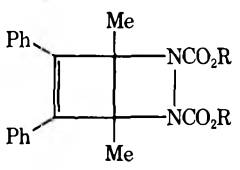

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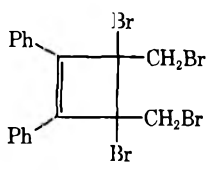


14

that of *cis*-stilbene, and for which a good model exists[15] in the compound **14**, which absorbs strongly at 288 nm (ϵ 19,500).

The isomerization of **5a** was reexamined by nmr spectroscopy at various stages before completion. The four peaks due to the intermediate noted earlier reached a maximum in 8 days reflux in carbon tetrachloride, which accounted for 40–45% of the total reaction material. The optimum yield (60%) and its rate of attainment (2 days) were enhanced by the use of refluxing acetonitrile as solvent. Separation by silica gel chromatography at this point gave a compound, mp 151–152°, whose elemental analysis showed it also to be an isomer of **5a**. Its spectral properties included C=N ir absorption at 1675 cm^{-1} and almost coincident methoxy peaks[6] in its nmr spectrum near τ 6.2, consistent with its formulation as the oxadiazine **6a**, the product of [3,3] sigmatropic rearrangement of **5a**.

The oxadiazines **6b–d** were obtained similarly, the optimum yields and reflux times being listed with their spectral properties in Table III. Acetonitrile was for all of them the solvent of choice. The transition state to **6**, involving bond formation from benzylic carbon to oxygen, may be more sensitive to solvent polarity than the transition state to **7**, in which the bond is formed to nitrogen, since charge separation is likely to be more acute.

(13) P. Bladon, S. McVey, and P. L. Pauson, *J. Chem. Soc.*, 306 (1966).
(14) L. J. Altman, M. F. Semmelhack, R. B. Hornby, and J. C. Vederas, *Chem. Commun.*, 686 (1968).
(15) A. T. Blomquist and Y. C. Meinwald, *J. Amer. Chem. Soc.*, **81**, 667 (1959).

The relationship between **5**, **6**, and **7** was clarified by refluxing the oxadiazine **6d** in tetrachloroethylene and monitoring the reaction by nmr analysis.[16] Table IV, in conjunction with the above results, clearly shows

TABLE IV

PROPORTIONS[a] OF **6d**, **5d**, AND **7d** IN REFLUXING TETRACHLOROETHYLENE[b]

Reflux time, hr	6d	5d	7d
0	100	0	0
0.25	86	14	0
0.50	54	46	0
1.8	33	59	8
7.0	26	55	19
17.5	20	42	38
35.5	0	24	76
70.0	0	2	98
94.0	0	0	100

[a] Estimated per cent by nmr analysis. [b] 0.2 *M* total concentration.

that **5** and **6** are in reversible equilibrium with one another and that the former is transformed slowly into **7**. The conversion of **6** into **7** either does not occur at all or is very much slower than that of **5** into **7**.

The isomerization of **5** to **7** was readily reversed by photolysis. Good yields of **5** were rapidly obtained from benzene solutions of **7** at 10° using a 150-W mercury lamp and a Pyrex filter. The optimum times and yields are shown in Table V.

TABLE V

PHOTOISOMERIZATION OF **7** (3.3×10^{-3} *M*) TO **5** IN BENZENE AT 10°

Compd	Time, hr	Yield[a] of **5**, %
7a	1.7	60–70
7b	3.0	55–65
7c	2.0	48–55
7d	20	75–80

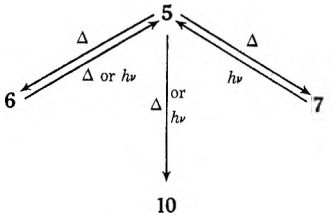
[a] Estimated by nmr analysis.

The oxadiazines **6** were stable to radiation above the Pyrex cut-off, but in quartz vessels their solutions in benzene were slowly isomerized, again to **5** (33% yield of **5a** after 30 hr, 43% of **5d** after 36 hr). The ROC=N chromophore, which must lie well below 300 nm, is presumably involved.

Both photolysis reactions were complicated by the instability of the product **5** to light, decarbonylation occurring to **10**.[17]

The generalized relationships between **5**, **6**, **7**, and **10** are indicated fully in Scheme I.

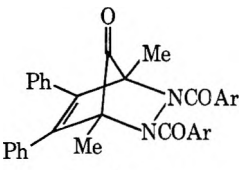
SCHEME I



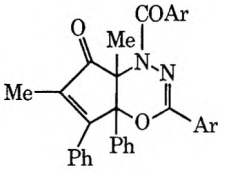
(16) The areas of the *C*-methyl protons were used. This was the most suitable oxidiazine, since it had no other absorptions in the high-field region of the spectrum.

(17) The product from photolysis of **6c** or **7c** was identical with **10c** obtained by heating **5c**. This and other reactions of the bridging carbonyl group in **5** are being currently studied in detail.

The destabilizing influence of the keto bridge is also evident in the Diels–Alder adducts derived from azodiaroyls. The cyclone **3** and *p*,*p*′-dinitroazodibenzoyl in refluxing methylene chloride gave a quantitative yield of the oxadiazine **16a**, mp 191.5–192.5°, with methyl singlets at τ 7.85 and 8.77 and λ at 247, 281, and 335 nm, data which respectively exclude the symmetrical adduct **15a** and the isomeric diazetidine (the chromophore of *p*-$NO_2C_6H_4C{=}N$ occurs at 335 nm[2]) as possible structures. Azodibenzoyl gave a glassy adduct **16b** with analogous properties, including singlets at τ 7.90 and 8.57 in benzene; when the reaction was run in benzene at room temperature an additional methyl singlet at τ 8.00 was observed in the nmr spectrum in the early stages of the reaction, which reached a mazimum of about 10% of the total methyl absorption. This may be attributed to the intermediacy of **15b**,[18] which is thus an exceedingly labile species.



15



16

a, Ar = *p*-$NO_2C_6H_4$
b, Ar = Ph

Discussion

All the isomerizations of the 1,2-diazabicyclo compounds described above are formally sigmatropic processes: **5** ⇄ **6** and **15** → **16** are [3,3] rearrangements (transfer of bond between C to N and C to O) and **5** ⇆ **7** is a [1,3] rearrangement (transfer of N between C and C). Most have carbocyclic counterparts involving [2.2.1]- and [3.2.0]bicycloheptene derivatives. Of these the thermal [3,3] rearrangements (Cope type) are fairly common[19] but thermal [1,3] examples are rare.[20] When the rearrangements are concerted, and hence subject to orbital symmetry rules,[21] the constraints of the bicyclic molecular framework require a suprafacial shift for both components in the former type, through a boat-like transition state,[22] and a suprafacial migration of carbon with inversion of configuration in the latter.

Photo-Cope reactions like **6** → **5** have not been described for the analogous carbocyclic systems, though they are known for others,[24] but photo [1,3] rearrange-

(18) Enhancement of the concentration of **15b** (bimolecular reaction) over that of the thermal isomer **16b** (unimolecular reaction) would be achieved by a high concentration of reagents. However, the unfavorable dissociation of the cyclone dimer and its modest solubility militate against this.

(19) *E.g.*, R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959); P. Yates and P. Eaton, *Tetrahedron*, **12**, 13 (1961); R. C. Cookson, J. Hudec, and R. O. Williams, *J. Chem. Soc. C*, 1382 (1967); M. T. Hughes and R. O. Williams, *Chem. Commun.*, 587 (1968); I. R. Bellobono, P. Beltrame, M. G. Cattania, and M. Simonetta, *Tetrahedron*, **26**, 4407 (1970).

(20) J. A. Berson, *Accounts Chem. Res.*, **1**, 152 (1968).

(21) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

(22) Less favored than the chair-like transition state normally utilized in acyclic systems by a $\Delta\Delta G^{\ddagger}$ of 5.5–6 kcal/mol in the range 225–250°.[23]

(23) W. von E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962); M. J. Goldstein and M. S. Benzon, *J. Amer. Chem. Soc.*, **94**, 7147 (1972).

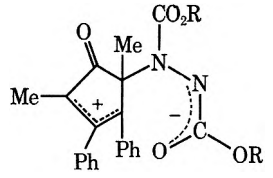
(24) O. L. Chapman and J. D. Lassila, *J. Amer. Chem. Soc.*, **90**, 2449 (1968); O. L. Chapman, M. Kane, J. D. Lassila, R. L. Loeschen, and H. E. Wright, *ibid.*, **91**, 6856 (1969); A. S. Kende, Z. Goldschmidt, and P. T. Izzo, *ibid.*, **91**, 6858 (1969); T. Sasaki, S. Eguchi, and M. Ohno, *ibid.*, **92**, 3193 (1970).

ments like 7 → 5 have ample precedent.[25] Most of these photoreactions are not concerted.

The application of orbital symmetry rules developed for carbocyclic systems to the thermal reactions of the heterocycles in the present work is of doubtful validity. In any event, these rules could not be utilized here as a proof of concertedness, since no stereochemical probe exists in any of these isomerizations to test them with. The [3,3] (hetero-Cope) rearrangements are confined by their geometry without stereochemical choice; the [1,3] rearrangement of 5 → 7 would involve, if concerted, inversion at the nitrogen, which is spontaneously rapid anyway.[26] Thus in the absence of other evidence (from kinetic and thermodynamic data or from trapping experiments) no conclusions can be drawn about the concertedness of the isomerizations.

The reacting frameworks in the isomerizations contain one kind (N) or two kinds (N and O) of heteroatom with nonbonded electron pairs, are substituted with charge and radical stabilizing groups (methyl, phenyl, acyl, or acyloxy) and experience a strong secondary interaction with the keto group.[28] Some of these features are evidently compatible with the operation of a concerted mechanism (though not necessarily one dictated by recognized orbital symmetry rules), as in the isomerization of 1 → 2 (R_1 = R_2 = H; R = Ph),[1] but the combination of all of them must greatly increase the likelihood of a stepwise mechanism.

A plausible intermediate in such a mechanism for the reversible processes of Scheme I is the dipolar species 17, ambident in both its cation and anion por-



→ 5, 6, or 7

tions, union of which in three of its four possible ways is observed in Scheme I. The driving force for its formation must lie particularly in the cation portion, namely, the stabilizing effect of the substituents and of the developing conjugation with the keto group, since the analogous adducts from cyclopentadiene are very stable.[3]

In the isomerization of the azodiaroyl adducts 15, though only a single, essential irreversible isomerization, to 16, is observed, a dipolar intermediate may still be involved (unlike the isomerization of the analogous adducts of cyclopentadiene, which are concerted[1]). The diazetidine isomeric with 15 and 16 may be thermodynamically less stable than either of them. The bulky *N*-aroyl groups would be sterically more demanding than the *N*-acyloxy groups of 7, which by virtue of the extra oxygen atom have a high degree of conformational flexibility and could allow the alkyl groups to occupy an uncrowded environment. Alternatively, or in addition, the inherent bond energy differences between isomeric oxadizines and diazetidines may weigh in favor of the former when derived from azodiaroyls and the latter when derived from azo esters.

Experimental Section

General Comments.—Melting points are uncorrected. Infrared spectra were recorded on a Beckman IR-10 and ultraviolet spectra on a Coleman EPS-3T Hitachi spectrometer. For the nuclear magnetic resonance spectra either a Varian T-60 or HA-100 instrument was used. Absorptions are quoted in τ values against tetramethylsilane as internal standard (abbreviations: s, singlet; d, doublet; t, triplet, q, quartet; m, multiplet). High-resolution mass spectra were obtained on a CEC21-110B or an AEI-MS9 spectrometer.

Azo Esters 4.—Di-2,2,2-trichloroethyl hydrazodicarboxylate was obtained from 2,2,2-trichloroethyl chloroformate by Rabjohn's method[33] (97%), and was recrystallized from aqueous ethanol, mp 101–102°. Oxidation with dinitrogen tetroxide[34] gave di-2,2,2-trichloroethyl azodicarboxylate, which crystallized as lemon-yellow plates (82%): mp 110–111° from benzene–hexane; ν (CCl_4) 1782 cm^{-1} (C=O); τ (CCl_4) 5.00 ppm (CH_2). This ester is stable indefinitely if stored in a desiccator in the dark.

Anal. Calcd for $C_6H_4Cl_6N_2O_4$: Cl, 55.86; N, 7.36. Found: Cl, 56.29; N, 7.41.

Dimethyl (4a), diethyl (4b), and diphenyl azodicarboxylate (4d) (orange plates, mp 122–123.5°, from benzene–hexane) were prepared similarly. Di-*tert*-butyl azodicarboxylate (4e) was purchased from Aldrich.

Cyclone 3.—Standard methods were used to convert 2,5-dimethyl-3,4-diphenyl-4-hydroxycyclopent-2-enone[9] to the dimer of 3[10] as well as to 1,4-dimethyl-2,3-diphenylcyclopentadiene.[13]

Dibromo Deivative of 3.—Condensation[35] of *p,p'*-dibromobenzil[36] with diethyl ketone gave 2,5-dimethyl-3,4-di-*p*-bromophenyl-4-hydroxycyclopent-2-enone. The mixture of epimeric carbinols was dehydrated[10] to the dimer of 1,4-dimethyl-2,3-di-*p*-bromophenylcyclopentadienone, which gave prisms, mp 180–182.5°, from methanol: ν (CCl_4) 1775, 1695 cm^{-1} (bridging, enone C=O); λ_{max} (EtOH) 236, 292 nm (ϵ 18,800, 13,500); nmr τ (CCl_4) 2.50–3.52 (m, 16, aromatic H), 7.88 (s, Me), 8.45 (s, Me), 8.83 (s, Me), 9.50 ppm (s, Me).

1,4-Dimethyl-5,6-diphenyl-2,3-carboalkoxy-2,3-diazabicyclo[2.2.1]hept-5-en-7-one (5) (See Table I).—The dimer of 3 (1.30 g, 2.5 mmol) and the azo ester 4 (5.01 mmol) were refluxed in carbon tetrachloride (40 ml), the progress of the reaction being monitored by nmr analysis, optimum yields of at least 90% being achieved. The solutions were then evaporated and worked up.

5a and 5d were crystallized from carbon tetrachloride in yields of 89 and 81%, respectively. 5a had λ_{max} (EtOH) 254 nm (shoulder, ϵ 9100).

Anal. Calcd for $C_{23}H_{22}N_2O_5$ (5a): C, 67.96; H, 5.46; N, 6.89. Found: 67.89; H, 5.49; N, 6.92.

5b, 5c, and 5d were noncrystalline. Each was purified by addition of hexane to an ethereal solution and allowing the gummy phase to settle out. The solvents were decanted and the residue was pumped *in vacuo* till it became brittle.

(25) L. S. Besford, R. C. Cookson, and J. Cooper, *J. Chem. Soc. C*, 1385 (1967); R. C. Cookson and D. C. Warrell, *ibid.*, 1391 (1967); R. L. Cargill, B. M. Gimarc, D. M. Pond, T. Y. King, A. B. Sears, and M. R. Willcott, *J. Amer. Chem. Soc.*, **92**, 3809 (1970).

(26) Amide nitrogen can be regarded as slightly pyramidal with rapid inversion and slow hindered rotation round the bond to the acyl group.[27]

(27) W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, **70**, 517 (1970), and references cited therein.

(28) As well as direct conjugation with the keto group present in 6 and 7 some interaction of the carbon–carbon double bond in 5 with the bridge is to be expected. Evidence for this in norborn-2-en-7-one is to be found in nmr,[29] ir,[30] uv,[31] and photoelectron[32] spectroscopy. Judging from the greater stability of 1 (R_1 = Ph; R_2 = Me; R = OMe)[3] than of 5 (R = Me), these interactions stabilize the transition state from 5 more than its ground state.

(29) Gurudata and J. B. Stothers, *Can. J. Chem.*, **47**, 3601 (1969).

(30) P. G. Gassman and W. M. Hooker, *J. Amer. Chem. Soc.*, **87**, 1079 (1965).

(31) R. E. Pincock and J. Hayward-Farmer, *Tetrahedron Lett.*, 4759 (1967); E. I. Snyder and B. Franzus, *J. Amer. Chem. Soc.*, **86**, 1170 (1964).

(32) D. Chadwick, D. C. Frost, and L. Weiler, *J. Amer. Chem. Soc.*, **93**, 4962 (1971).

(33) N. Rabjohn, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 375.

(34) J. C. Stickler and W. H. Pirkle, *J. Org. Chem.*, **31**, 3444 (1966).

(35) The use of Triton B as catalyst was an excellent variant on the usual aqueous sodium hydroxide.[9]

(36) H. Biltz, *Chem. Ber.*, **41**, 1761 (1908).

1,3-Dimethyl-4,5-diphenyl-6,7-dicarboalkoxy-6,7-diazabicyclo[3.2.0]hept-3-en-2-one (7) (See Table II). A.—The adducts **5** (5.0 mmol) were refluxed in tetrachloroethylene (40 ml) for 4 days, or, in the case of **5a**, in bromobenzene for 5 hr, and the solutions were then evaporated.

7a (>95% by nmr, 85% after crystallization) had *m/e* (rel intensity) 406.1522 (3, P^+, calcd 406.1524), 275.1546 (48, $C_{19}H_{19}N_2^+$, calcd 275.1558), 260.1196 (100, $C_{18}H_{16}O^+$, calcd 260.1201).

Anal. Calcd for $C_{23}H_{22}N_2O_5$: C, 67.96; H, 5.46; N, 6.89. Found: 67.86; H, 5.67; N, 7.04.

7b was obtained in >95% yield by nmr (85% after crystallization).

Anal. Calcd for $C_{25}H_{26}N_2O_5$: C, 69.11; H, 6.03; N, 6.45. Found: 69.27; H, 5.86; N, 6.42.

7c was obtained in *ca.* 50% yield by nmr (40% after crystallization). Addition of methanol (15 ml) caused separation of the crystalline diazetidine.

Anal. Calcd for $C_{25}H_{20}Cl_6N_2O_5$: Cl, 33.18; N, 4.37. Found: Cl, 32.95; N, 4.22.

7d was obtained in 85–90% yield by nmr (72% after crystallization).

7e could not be positively identified among the complex tarry products resulting from long heating of **5e** in tetrachloroethylene.

B. Alternate Synthesis of 7a.—A solution of the dimer of **3** (1.30 g, 2.5 mmol) and **4a** (0.73 g, 5.01 mmol) in bromobenzene (20 ml) was refluxed for 5 hr. Evaporation and crystallization of the residue from methanol gave **7a** (85%).

Ditrichloroethyl 3,6-Dimethyl-4,5-diphenyl-1,2-dihydropyridazine-1,2-dicarboxylate (10c).—The methanolic mother liquor from the separation of the crystalline diazetidine **7c** was reduced to half its volume and refrigerated for 24 hr. Crystalline **10c** separated as colorless prisms (34%): mp 123–124°; ν (CCl_4) 1740 cm^{-1}; λ_{max} (EtOH) 245 nm (ϵ 17,300) and broad shoulder (ϵ 4000 at 295 nm); nmr ($CDCl_3$) τ 3.0 (broad s, 10 phenyl H), 5.08 (AB q, 2 CH_2, J_{AB} = 12 Hz), 7.76 ppm (s, 2 Me).

Anal. Calcd for $C_{24}H_{20}Cl_6N_2O_4$: Cl, 34.69; N, 4.57. Found: Cl, 34.32; N, 4.56.

1,4-Dimethyl-5,6-di-*p*-bromophenyl-2,3-dicarbomethoxy-2,3-diazabicyclo[2.2.1]hept-5-en-7-one.—A solution of the dibromo derivative of **3** as its dimer (4.18 g, 5 mmol) and **4a** (1.46 g, 10 mmol) in carbon tetrachloride (250 ml) was refluxed for 30 hr, concentrated (50 ml), and refrigerated. The adduct slowly separated over 1 day, and was collected and recrystallized from carbon tetrachloride–pentane as prisms (80%): mp 111–113°; ν (CCl_4) 1800, 1750, 1725 cm^{-1} (bridging, ester C=O); nmr (CCl_4) τ 2.5–3.2 (m, q predominating, 8 aromatic H), 6.41 (s, OMe), 8.38 ppm (s, CMe).

Anal. Calcd for $C_{23}H_{20}Br_2N_2O_5$: Br, 28.37. Found: Br, 28.77.

1,3-Dimethyl-4,5-di-*p*-bromophenyl-6,7-dicarbomethoxy-6,7-diazabicyclo[3.2.0]hept-3-en-2-one (9). A.—The progress of the isomerization of the adduct (5.64 g, 10 mmol) in refluxing bromobenzene (40 ml) was monitored by nmr analysis of the methyl region. After 5 hr the two original methyl peaks had disappeared and the spectrum was consistent with the presence of the diazetidine **9** (85%) and a symmetrical compound (15%), perhaps the product of decarbonylation of the adduct. Evaporation and addition of methanol (15 ml) gave crystalline diazetidine which was recrystallized from ethanol as prisms: mp 198–199°; ν (CCl_4) 1770, 1741, 1723 cm^{-1} (two ester, enone C=O); λ_{max} (MeOH) 290 nm (ϵ 13,700); nmr ($CDCl_3$) τ 2.3–3.2 (m, 8, aromatic H), 6.20 (s, CO_2Me on N-7), 6.90 (s, CO_2Me on N-6), 7.90 (s, vinyl Me), 8.83 ppm (s, *tert*-Me); *m/e* (rel intensity) 564 (1, P^+ due to $C_{23}H_{20}{}^{79}Br^{81}BrN_2O_5^+$), 432.9728 (27, $C_{19}H_{17}{}^{79}Br^{81}BrN_2^+$, calcd 432.9738), 418 (100, due to $C_{19}H_{14}{}^{79}Br^{81}BrO^+$).

Anal. Calcd for $C_{23}H_{20}Br_2N_2O_5$: C, 48.94; H, 3.55; Br, 28.37; N, 4.97. Found: C, 48.70; H, 3.65; Br, 28.70; N, 5.08.

B.—The cyclone and the azo ester (1 mmol each) were refluxed in solution in bromobenzene for 7 hr. The solvent was removed and the solid residue was crystallized from methanol to give the diazetidine (85%), mp 198.5–199.5°.

***cis*-2-Alkoxy-4-carboalkoxy-4a,6-dimethyl-7,7a-diphenyl-4,4a,5,7a-tetrahydrocyclopenta-1,3,4-oxadiazin-5-one (6) (See Table III).** A.—A solution of **5a** (0.406 g, 1.0 mmol) was refluxed in carbon tetrachloride (6 ml) and the reaction was followed by nmr spectroscopy. A maximum yield (40–45%) of the desired product **6a** was obtained in about 8 days. With the same concentration in refluxing acetonitrile a maximum of 60% was obtained in 55 hr. Longer reflux times caused build-up of substantial amounts of **7a**.

The acetonitrile run was scaled up (10 mmol) and the solution was refluxed for 55 hr and evaporated. The residue was chromatographed on silica gel from petroleum ether (bp 60–80°)–ether (1:4). A small amount of the diazetidine **7a** was eluted first, then the main fraction, the oxidiazine **6a** (50%), and finally unreacted **5a**. Recrystallization of **6a** from ether–hexane gave prisms, mp 151–152°.

Anal. Calcd for $C_{23}H_{22}N_2O_5$: C, 67.86; H, 5.46; N, 6.89. Found: C, 67.54; H, 5.54; N, 7.07.

The remaining adducts were similarly refluxed in acetonitrile at the same concentrations, and the reaction products were purified by silica gel chromatography.

6b and **6c** were both glassy solids which resisted crystallization.

6d crystallized from petroleum ether (bp 30–60°)–carbon tetrachloride, mp 161–162°.

Anal. Calcd for $C_{33}H_{26}N_2O_5$: C, 74.70; H, 4.94; N, 5.28. Found: C, 74.42; H, 5.03; N, 5.56.

There was no conclusive evidence of the formation of **6e** after reflux for 8 days. The nmr spectrum of the substrate was very complex.

B. Alternative Synthesis of 6a.—The dimer of **3** (1.30 g, 2.5 mmol) and **4a** (0.73 g, 5 mmol) were refluxed in acetonitrile for 60 hr. Work-up and chromatography as before gave **6a** (50%).

Thermal Isomerization of 6d to 5d and 7d.—A solution of the oxadiazine **6e** (1.0 g, 1.9 mmol) in tetrachloroethylene (10 ml) was refluxed and periodically analyzed by nmr spectroscopy by noting the changes in the methyl group absorptions. The proportions were determined by repeated integration. The results are shown in Table IV.

Photochemical Reactions. A. Photoisomerization of 7 to 5.—The details for **7a** are typical. A solution of **7a** (0.203 g, 0.5 mmol) in dry benzene (150 ml), water-jacketed at 10°, was irradiated through Pyrex with a 125-W Hanovia uv immersion lamp. The reaction was followed by noting the appearance of the bridging carbonyl absorption at 1800 cm^{-1} in the ir and the methyl group absorption at τ 8.2 in the nmr spectrum, both characteristic of **5a**. After 100 min, the optimum time (60–70% yield by nmr analysis), the solution was evaporated and the residue was twice crystallized from carbon tetrachloride–pentane to give **5a**, mp 116–117°, alone or in admixture with authentic adduct.

Longer reflux times led to the appearance of a new methyl absorption in the nmr spectrum, attributable to the product of decarbonylation, **10a**.

The optimum times and yields for the photolysis of the other diazetidines **7b–d** are given in Table V.

When the photolysis of **7c** was extended to 6 hr, the solution evaporated, and the residue purified by chromatography on silica gel, the decarbonylated product **10c** was obtained as a glassy solid (40%). It slowly crystallized from methanol as colorless prisms, mp 123–124°, identical in all respects (spectra, mixture melting point) with the by-product in the thermal isomerization of **5c**.

B. Photoisomerization of 6 to 5.—The reaction was carried out only with the crystalline oxadiazines **6a** and **6d**. The scale, concentration, solvent, light source, and temperature were the same as in A. No reaction occurred over a period of many days when a Pyrex filter was used.

Isomerization occurred slowly in a quartz vessel, the bridging carbonyl and the methyl group of **5** being detectable as before. The optimum yield from **6a** was 30–35% after 30 hr. Evaporation and separation by silica gel chromatography (as described for the products from thermal isomerization of **5a**) gave **5a** identical in all respects with authentic adduct.

A 40–45% yield of **5d** was obtained from **6d** after 36 hr. The product was obtained directly by crystallization of the residue from carbon tetrachloride.

In either case longer reflux times led to decarbonylation of the product.

***cis*-2-Aryl-4-aroyl-4a,6-dimethyl-7,7a-diphenyl-4,4a,5,7a-tetrahydrocyclopenta-1,3,4-oxadiazin-5-one (16).** A. **16a.**—A solution of the dimer of **3** (1.30 g, 2.5 mmol) and azodi-*p*-nitrobenzoyl[2] (1.64 g, 5 mmol) in methylene chloride (20 ml) was refluxed for

20 hr, and the solvent was evaporated. The residue had spectra essentially identical with those of **16a**, obtained by crystallization first from methanol–acetone, then from benzene–pentane, as pale yellow prisms (72%): mp 191.5–192.5°; ν (Nujol) 1730, 1683, 1652 cm^{-1} (enone, aroyl CO, C=N); λ_{max} (EtOH) 247, 281, 335 nm (ϵ 17,000, 23,200, 10,900); nmr ($CDCl_3$) τ 1.6–3.0 (m, 18, aromatic H), 7.85 (s, vinyl Me), 8.77 ppm (*tert*-Me).

Anal. Calcd for $C_{33}H_{24}N_4O_7$: C, 67.11; H, 4.44; N, 9.49. Found: C, 67.40; H, 4.56; N, 9.41.

B. 16b.—The reaction of the dimer of **3** (2.60 g, 5 mmol) with azodibenzoyl (2.38 g, 10 mmol) in refluxing benzene (50 ml) was monitored at 30-min intervals. After 10 hr the four methyl singlets of the dimer had been completely replaced by the two methyl singlets of **16b**, which was obtained as a glass, in high purity, on evaporation. An analytical sample was prepared by slowly adding hexane with stirring to a solution in benzene. The solvents were decanted and the residue on standing *in vacuo* became brittle; ν (CCl_4) 1732, 1665 cm^{-1} (enone and benzoyl C=O, C=N); λ_{max} (EtOH) 280 nm (ϵ 25,100); nmr (CCl_4) τ 2.0–3.2 (20, aromatic H), 7.85 (s, vinyl Me), 8.20 ppm (s, *tert*-Me).

Anal. Calcd for $C_{33}H_{26}N_2O_3$: C, 79.55; H, 5.26; N, 5.62. Found: C, 79.50; H, 5.40; N, 5.50.

A solution of the dimer of **3** and azodibenzoyl in benzene at the same concentration as above was kept at room temperature and the reaction was monitored by nmr analysis. As well as the two singlets at τ 7.90 and 8.57 due to the oxadiazine **16b**, a singlet was also evident at 8.00, attributable to **15b**, in the early stages of the reaction. It reached a maximum of about 10% of the total methyl absorption in 3 days.

Both **16a** and **16b** were stable to prolonged refluxing in bromobenzene.

Registry No.—**3** dimer, 38883-84-0; **3** *p*-bromophenyl dimer, 38883-85-1; **4a**, 2446-84-6; **4b**, 1972-28-7; **4c**, 38857-88-4; **4d**, 2449-14-1; **4e**, 870-50-8; **5a**, 38857-91-9; **5b**, 38857-92-0; **5c**, 38857-93-1; **5d**, 38857-94-2; **5e**, 38857-95-3; **6a**, 38864-11-8; **6b**, 38864-12-9; **6c**, 38864-13-0; **6d**, 38864-14-1; **7a**, 38857-96-4; **7b**, 38857-97-5; **7c**, 38857-98-6; **7d**, 38857-99-7; **9**, 38789-27-4; **10c**, 38858-01-4; **16a**, 38864-15-2; **16b**, 38864-16-3; di-2,2,2-trichloroethyl hydrazodicarboxylate, 38858-02-5; 1,4-dimethyl-5,6-di-*p*-bromophenyl-2,3-dicarbomethoxy-2,3-diazobicyclo[2.2.1]hept-5-en-7-one, 38858-03-6; azodi-*p*-nitrobenzoyl, 35630-50-3; azodibenzoyl, 959-31-9.

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Studies in the Imidazo[1,5-*a*]pyrazine System[1]

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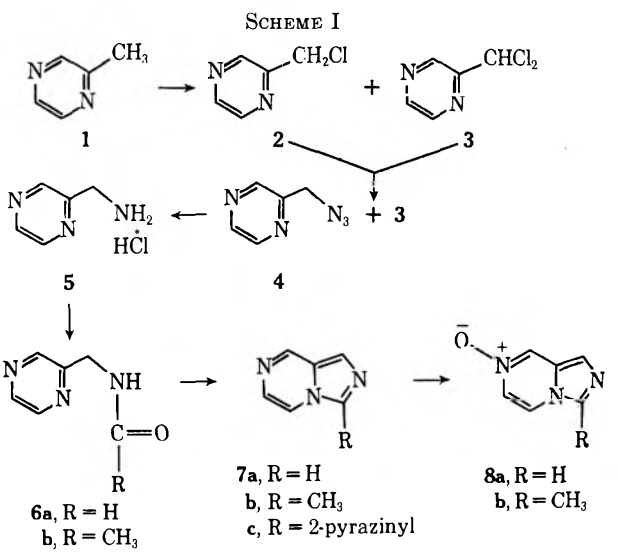
A general synthesis of imidazo[1,5-*a*]pyrazines as well as nmr studies on some derivatives is reported.

The first synthesis of an imidazo[1,5-*a*]pyrazine was reported recently using a novel reaction between pyrazine carboxaldehyde and ammonium chloride to give the 3-(2-pyrazinyl) derivative **7c**.[2] This method, however, cannot be used to prepare the parent heterocycle **7a** or alkyl-substituted derivatives such as **7b**, compounds in which we were interested as sources of imidazo[1,5-*a*]pyrazines that contained a variety of functional groups. This paper describes a general approach to such compounds and nmr studies that permit the identification of each of the protons in the heterocyclic system, an important consideration in assigning the structures of electrophilic substitution products of these heterocycles.

A key intermediate in our synthetic approach (Scheme I) was 2-aminomethylpyrazine. This rather unstable material has been reported previously derived from chloromethylpyrazine (**2**) using potassium phthalimide[3] but with very low yields, and this agrees with our observations of this method. We modified this procedure by utilizing the hydrolysis of the hexamine salt[4] prepared from **2** and hexamethylenetetramine, but again the yields were low and erratic. A practical route to **5** was available, however, by catalytic reduction of azidomethylpyrazine (**4**), which could be prepared,

SCHEME I



in good yield, from the reaction of **2** and sodium azide. Chloromethylpyrazine (**2**), prepared by the reaction of *N*-chlorosuccinimide with methylpyrazine (**1**),[5] was contaminated with dichloromethylpyrazine (**3**), which carries over as a contaminant in the formation of azide **4**. Pure **4** was obtained only after three distillations, in poor and impractical overall yield. Hydrogenation of the pure azide **4** furnished the amine, which was isolated as a hydrochloride salt (**5**) in 75% yield, but this repre-

(1) This work was carried out under the auspices of the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Public Health Service Contract No. NIH-71-2312.

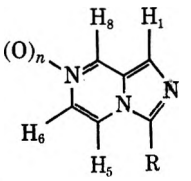
(2) E. Abushanab, *Tetrahedron Lett.*, 1441 (1971).

(3) A. Hirschberg and P. G. Mattner, *J. Med. Chem.*, **11**, 911 (1968).

(4) S. J. Angyal, *Org. React.*, **8**, 181 (1954).

(5) A. Hirschberg and P. E. Spoerri, *J. Org. Chem.*, **26**, 2356 (1961).

TABLE I



	δ, ppm			δ, ppm		
	7a, R = H; n = 0	8a, R = H; n = 1	Δδ	7b, R = CH_3; n = 0	8b, R = CH_3; n = 1	Δδ
H_1	7.83 (s)	7.63 (s)	−0.20	7.64 (s)	7.40 (s)	−0.24
H_3	8.28 (s)	8.25 (s)	−0.03	2.61 (s, CH_3)	2.61 (s, CH_3)	0
H_5	7.58 (d), $J_{5,6}$ = 5 Hz	7.97 (m)	+0.41	7.45 (m), $J_{5,6}$ = 5 Hz	7.73 (d), $J_{5,6}$ = 6 Hz	+0.28
H_6	7.91 (m)	7.38 (q), $J_{5,6}$ = 5, $J_{6,8}$ = 1 Hz	−0.53	7.58 (m), $J_{5,6}$ = 5, $J_{1,6}$ = 1, $J_{6,8}$ = 1.6 Hz	7.23 (q), $J_{5,6}$ = 6, $J_{6,8}$ = 1.8 Hz	−0.35
H_8	9.03 (s)	8.56 (m)	−0.47	8.86 (d), $J_{6,8}$ = 1.6 Hz	8.41 (d), $J_{6,8}$ = 1.8 Hz	−0.45

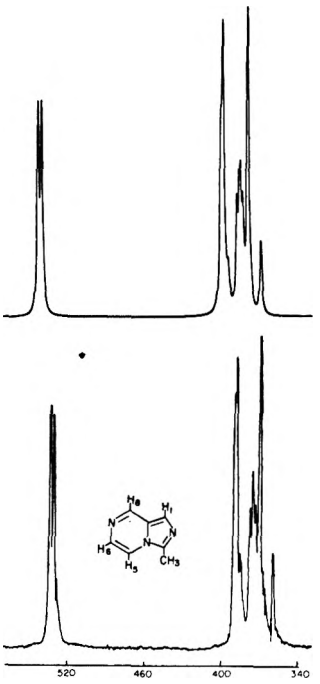


Figure 1.—Nmr spectrum of **7b**: relative δ 171.3 (H_1), 183 (H_5), 176.5 (H_6), and 100 Hz (H_8); theoretical $J_{1,6}$ = 1.0, $J_{6,8}$ = 1.6, $J_{5,6}$ = 5 Hz; T_2 = 0.37 sec.

sents an overall yield of **5** from **2** of 1.6%. Fortunately, a reproducible and more practical procedure was discovered which involves the hydrogenation of a mixture of **4** and **3**. Hydrogenolysis of **3** provided hydrogen chloride, at apparently the proper rate, that trapped the generated amine as the hydrochloride **5** in an overall yield from **2** of 63%. Under our synthetic conditions there was no tendency for hydrogenation of the pyrazine ring, a problem that we had anticipated might plague this approach. It is interesting that attempts to substitute chloroform[6] as the hydrogen chloride precursor or to deliberately add hydrogen chloride in the hydrogenation of distilled **4** that contained very small amounts of **3** were not successful and led to an unpurified product.

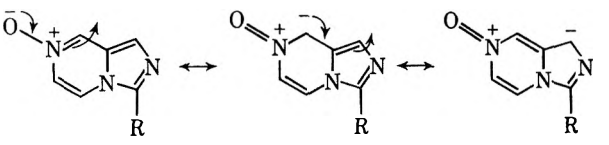
Reaction of the free base prepared from **5** with formic acid gave the formamide **6a**, while reaction with acetic anhydride yielded the acetamide **6b**. Cyclodehydration of the amides with neat phosphoryl chloride afforded the heterocycles **7a** and **7b**, respectively. When these imidazo[1,5-*a*]pyrazines were treated with *m*-chloroperbenzoic acid, the 7-*N*-oxides (**8a** and **8b**, respectively) resulted. The nmr spectra (discussed below) of **7a**, **7b**, **8a**, and **8b** permitted the assignment of the position of oxidation as N-7.

Nmr Spectra.—Chemical shifts and coupling constants for **7a**, **7b**, **8a**, and **8b** are listed in Table I.

The position of the oxygen in **8b** was based on the lack of changes of the chemical shift of the methyl group. A downfield shift would have been observed had oxidation taken place at N-2 or N-4.[7] Further, it is known from literature data[8] that N-oxidation results in an upfield shift of the protons on carbons adjacent to the *N*-oxide function with a downfield shift for protons on carbons which are once removed from the *N*-oxide. These considerations permitted unambiguous assignment in the spectrum of **8b** to H-5. Protons H-5, H-6, and H-8 formed an ABX system in **7b** and irradiation at the low-field doublet (δ 8.86) simplified the spectra such that assignments for H-6 and H-8 could be made. These decoupling studies revealed an unusual long-range coupling over six bonds between H-6 and H-1; in structurally related systems similar five-bond long-range couplings have been observed.[9] Further confirmation of these assignments was obtained by a calculation of the nmr spectrum of **7b** using computer program No. 140, DNMR (Quantum Chemistry Program Exchange). The results are shown in Figure 1.

The nmr studies on **7a** and its *N*-oxide **8a** (Table I) were completely analogous; the essential identity of the chemical shift of H-3 in both compounds is noteworthy.

It is interesting in both **8a** and **8b** that H-1 experiences a shielding effect by the *N*-oxide similar to its effect on H-8. It seems likely that the oxygen can furnish electrons to either position by the electronic shifts depicted in structures **9** and **10**.



9 **10**

(6) While our work was in progress, J. A. Secrist, III, and M. W. Logue, *J. Org. Chem.*, **37**, 335 (1972), reported that hydrogenation of amine precursors in the presence of chloroforom permitted the trapping of certain unstable amines as their hydrochloride salts.

(7) W. H. Grumprecht, T. E. Benkelman, and R. Poju, *J. Org. Chem.*, **29**, 2477 (1964).

(8) L. M. Jackman and S. S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Elmsford, N. Y., 1969, pp 209–212.

(9) W. W. Paudler, "Nuclear Magnetic Resonance," Allyn and Bacon, Boston, Mass., 1971, pp 144, 145.

Investigations of electrophilic subsitution reactions of **7a** and **7b** are in progress and will be reported at a later date.

Experimental Section

Melting points (uncorrected) were determined with a Thomas-Hoover capillary apparatus. Nmr spectra were determined on a Varian A-60 apparatus or on a JEOLCO C-60-HL instrument. Ultraviolet spectral measurements were obtained in 95% ethanol using a Spectronic 505 instrument. Mass spectral molecular weights were obtained from either a Perkin-Elmer RMV-6E or a CEC 24-104 spectrometer. All evaporations were conducted *in vacuo* using either a water aspirator or a vacuum pump.

Chloromethylpyrazine (2).—The procedure followed was essentially that of Hirschberg and Spoerri[5] with some changes in the ratio of reagents that were found to improve the conversion to **2**. A mixture of 50.0 g (0.51 mol) of methylpyrazine (**1**), 90.0 g (0.68 mol) of *N*-chlorosuccinimide, 0.8 g of benzoyl peroxide, and 1500 ml of carbon tetrachloride was refluxed, with stirring, for 16 hr, then cooled to 0°, and the succinimide separated by filtration, using 250 ml of carbon tetrachloride for washing. The residual oil weighed 59.2 g and was shown by nmr analysis to contain **1**, **2**, and dichloromethylpyrazine (**3**) in a weight ratio of 1:4.16:1, indicating a yield of **2** of 40 g (58.7%) with no allowance for unchanged **1**.

Azidomethylpyrazine (4).—The above-described sample of **2** was dissolved in 700 ml of acetonitrile, a solution of 29.5 g (0.50 mol) of sodium azide in 150 ml of water was added, and the mixture was heated at reflux, with stirring, for 12 hr, concentrated to *ca.* 200 ml, diluted with 200 ml of water, and extracted with four 300-ml portions of ether. The combined extracts were washed with two 150-ml portions of water, dried over sodium sulfate, and evaporated to leave a residue that was vacuum distilled, collecting 50 g of distillate at 55–62° (0.6 mm). Analysis by nmr indicated the weight ratios of **4** to **3** to be 4:1, giving a yield of **4** of 40.3 g (95%). Repeated fractional distillation of a mixture of **4** and **3** (3:1, 70 g) using a 6-in. Vigreux column furnished 1.1 g of the pure azide **4**, bp 65° (1.0 mm), for an overall recovery of 2.2% of the available azide.

Anal. Calcd for $C_5H_5N_5$: C, 44.44; H, 3.73; N, 51.83. Found: C, 44.45; H, 3.98; N, 51.62.

Aminomethylpyrazine Hydrochloride (5). **A.**—A 10-g portion of the above mixture containing **4** and **3** in a ratio of 4:1, dissolved in 200 ml of 95% ethanol, was hydrogenated at 3–4 atm over Adams catalyst (150 mg) with flushing of the system with hydrogen to sweep out the nitrogen formed at 0.5-hr intervals. About 5.5 hr was required to complete the reduction. Then 15 ml of ethanolic hydrogen chloride (12% v/v) was added and the catalyst was removed by filtration. The solvent was evaporated and the solid residue was crystallized twice from methanol–chloroform to yield 5.2 g (65%) of colorless plates, mp 183–184°. The mass spectrum exhibited a molecular ion at *m/e* 109, corresponding to that of the free amine.

Anal. Calcd for $C_5H_7N_3 \cdot HCl$: C, 41.28; H, 5.54; N, 28.88; Cl, 24.36; mol wt, 145.5. Found: C, 41.38; H, 5.54; N, 28.67; Cl, 24.32.

B.—Following the above procedure, azidomethylpyrazine (**4**, 1.0 g) was dissolved in 95% ethanol (50 ml) and hydrogenated over platinum oxide (15 mg) for 2 hr. Filtration followed by the addition of ethanolic hydrogen chloride (2.7 ml, 10% v/v) and evaporation of the solvent gave a solid residue of **5**, 0.84 g (75.6%), mp 174–175°. One recrystallization from methanol–chloroform furnished the pure hydrochloride **5**, mp 183–184, identical in all respects (mixture melting point, ir, tlc) with the analytical sample.

***N*-Formylaminomethylpyrazine (6a).**—A solution of 14.5 g (0.10 mol) of **5** in 15 ml of methanol was treated with a solution of 6.6 g (0.10 mol) of 85% potassium hydroxide in 15 ml of methanol. The mixture was evaporated and the residue was extracted with three 200-ml portions of dichloromethane. The combined extracts were dried over sodium sulfate and evaporated, leaving 10.9 g of liquid which was mixed with 30 ml of 97% formic acid, and the resulting solution was heated for 2 hr on the steam bath, then diluted with 15 ml of benzene and heated under reflux for 16 hr more. The solution was evaporated and the residue was vacuum distilled to give 12 g (87%) of a pale yellow oil at 113–114° (0.06 mm). On standing the distillate changed to a solid, mp 39–40°.

Anal. Calcd for $C_6H_7N_3O$: C, 52.55; H, 5.10; N, 30.69; mol wt, 137. Found: C, 52.65; H, 5.35; N, 30.36; mol wt, 137.

***N*-Acetylaminomethylpyrazine (6b).**—The hydrochloride **5** (14.5 g, 0.10 mol) dissolved in 15 ml of methanol was converted to its free base with potassium hydroxide as described for the preparation of **6a** but without evaporation of the methanolic solution. To the ice-cold methanolic solution of the amine was added, slowly, 15.5 g (0.15 mol) of acetic anhydride over a period of 10 min. Then a solution of 6.6 g (0.10 mol) of 85% potassium hydroxide in 15 ml of methanol was added over a 15-min period and this was followed by the addition of a further quantity (15.5 g) of acetic anhydride. After the reaction mixture had stood at room temperature for about 16 hr, it was concentrated to about 30 ml. Water (30 ml) was added and the solution was extracted with three 150-ml portions of dichloromethane. The combined extracts were dried over potassium carbonate, filtered, and evaporated to leave 15 g (quantitative yield) of solid residue that was homogeneous according to thin layer chromatography (tlc). Crystallization from ether furnished **6b** as colorless needles, mp 64°.

Anal. Calcd for $C_7H_9N_3O$: C, 55.63; H, 6.00; N, 27.81; mol wt, 151. Found: C, 55.40; H, 6.17; N, 27.80; mol wt, 151.

Imidazo[1,5-*a*]pyrazine (7a).—The formamide **6a** (1.0 g) was slowly added to phosphoryl chloride (5 ml) using cooling with an ice–methanol bath. The reaction mixture was then heated on a steam bath for 30 min and evaporated. The residue was washed with 50 ml of hexane, then dissolved in 5 ml of water. The pH was adjusted to 9 with 20% aqueous sodium hydroxide and the solution was extracted with four 150-ml portions of chloroform. The combined extracts were washed with 20 ml of water, dried over sodium sulfate, and evaporated to leave 0.87 g of residue which was crystallized three times from ether–hexane to afford 0.30 g (35%) of **7a** as pale yellow needles: mp 103–104°; uv max 269 nm (log ϵ 3.523), 280 (3.502), and 331 (3.331) with shoulders at 260 (3.414) and 263 (3.431).

Anal. Calcd for $C_6H_5N_3$: C, 60.50; H, 4.20; N, 35.29; mol wt, 119. Found: C, 60.16; H, 4.42; N, 35.02; mol wt, 119.

3-Methylimidazo[1,5-*a*]pyrazine (7b).—The procedure followed was essentially that for preparation of **7a** except that the phosphoryl chloride solution was heated for 1 hr. The crude product (0.80 g, 90% yield) was homogeneous according to tlc and was crystallized from ether–hexane to afford 0.60 g (67%) of **7b** as pale yellow needles: mp 142–143°; uv max 270 nm (log ϵ 3.647), 281 (3.611), and 340 (3.425) with shoulders at 260 (3.550) and 265 (3.571).

Anal. Calcd for $C_7H_7N_3$: C, 63.16; H, 5.26; N, 31.58; mol wt, 133. Found: C, 62.84; H, 5.38; N, 31.31; mol wt, 133.

Imidazo[1,5-*a*]pyrazine 7-Oxide (8a).[10]—To a solution of 5.0 g (42 mmol) of **7a** in 150 ml of chloroform was added 12.5 g (72 mmol) of *m*-chloroperbenzoic acid in 150 ml of chloroform. The mixture was stirred at room temperature for 30 min and then heated at reflux for 15 min. The solution was cooled to room temperature and filtered, and the filtrate was evaporated. The residue separated using dry-column chromatography on a 3.8 × 80 cm column of neutral alumina (30 g to which 3 g of water was added) using chloroform–methanol (94:6 v/v) for elution. The starting material, 0.5 g, was obtained from the initial fractions and this was followed by 0.40 g (9.8% yield based on consumed starting material) of the *N*-oxide **8a**, mp 170°, ir ($CHCl_3$), 1305 cm^{-1} (strong, characteristic of *N*-oxides). The mass spectrum showed a molecular ion at *m/e* 135 followed by a fragment indicating the loss of oxygen at *m/e* 119 ($M^+ - 16$).

3-Methylimidazo[1,5-*a*]pyrazine 7-Oxide (8b).[10]—The procedure used was identical with that described for the preparation of **8a**. The heterocycle **7b**, 4.0 g (30 mmol), was treated with 19.5 g (120 mmol) of *m*-chloroperbenzoic acid in 300 ml of chloroform. The solution was cooled to room temperature, filtered, and evaporated. The residue was adsorbed on neutral alumina (30 g + 3 ml of water) using methylene chloride, and was chromatographed on a dry column (3 × 40 cm) eluting with chloroform–methanol (98:2 v/v). The starting material, 0.9 g, was obtained from the initial fractions (1 l.) followed by **8b** (2.0 g, 58% based on consumed starting material). Crystallization from chloroform–ether gave the *N*-oxide **8b** as pale yellow needles,

(10) Although these two compounds were homogeneous by tlc and had sharp melting points, no acceptable elemental analyses for them could be obtained. Repeated crystallization resulted in progressively larger deviation from the calculated values, suggesting the instability of these compounds.

mp 165–166°. The mass spectrum similarly showed a molecular ion at m/e 149 followed by m/e 133 ($M^+ - 16$).

Registry No.—**1**, 1632-76-4; **2**, 39204-47-2; **4**, 39204-48-3; **5**, 39204-49-4; **6a**, 39204-50-7; **6b**, 39204-51-8; **7a**, 274-49-7; **7b**, 39204-53-0; **8a**, 39204-54-1; **8b**, 39204-55-2.

Acknowledgments.—The authors wish to thank Dr. Yuzuru Shimizu for the mass spectral determinations, and Mr. David Dauplaise for the nmr analyses. Many of the nmr spectra were determined on an instrument for which the National Science Foundation GP-28408 furnished partial financial support.

Acid-Promoted Aromatic Substitution Processes in Photochemical and Thermal Decompositions of Aryl Azides

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Photolysis of aryl azides in 50:4 mesitylene–trifluoroacetic acid (TFA) gives substantial amounts of diphenylamines derived from electrophilic substitution of the mesitylene. Products derived from ring expansion of an aryl nitrene intermediate are also observed. Thermal decomposition of aryl azides at about 85° in the same medium leads to increased yields of diphenylamines. The substitution reaction is not limited to mesitylene but also is observed in *p*-xylene, anisole, and toluene. No substitution product could be isolated in the case of benzene. Mechanistic interpretation of these results is offered.

We have observed that the course of deoxygenation of aromatic nitro and nitroso compounds is profoundly affected by the presence of carboxylic acids in the reaction medium. This was first noted[1] when it was observed that the presence of 5% acetic acid in the triethyl phosphite medium used for photochemical deoxygenation of aromatic nitro compounds substantially diverted the reaction from the normal product, triethyl *N*-arylphosphorimidates, to aromatic nucleophilic substitution products including *o*-hydroxyacetanilides and *o*- and *p*-aminophenylphosphonates. The chemical deoxygenation of aromatic nitroso compounds showed a similar response to the presence of acetic acid in the reaction medium.[1] Later, the deoxygenation of nitrosobenzenes in alcoholic solvents was shown to be very sensitive to solvent acidity. For example, although deoxygenation of nitrosobenzene in pure ethanol resulted in neglible yield of *o*- and *p*-phenetidines, identical reaction mixtures containing 0.02 mol % acetic acid in the ethanol gave rise to >60% yield of the phenetidines.[2]

In order to further define the role that proton donors might play in determining the fate of phenylnitrene and related intermediates on the C_6H_5N energy surface[3] we have studied the photochemical decomposition of several aryl azides in aromatic solvents containing trifluoroacetic acid (~7.5% by volume). We observe aromatic substitution under these conditions and we consider the substitution process to be mechanistically distinct both from the aryl nitrenium[1,2,4] and aryl nitrene[5] pathways for aromatic substitution.

Results

A. Photochemical Reactions.—The present study was concentrated largely on the system mesitylene–TFA. There are significant differences in the distribution of minor products from the individual azides. However, some unifying reactivity patterns emerge. Most important is the formation of diarylamines from each of the azides, usually in substantial yield. Scheme I and Table I summarize the yield data.

SCHEME I[a]

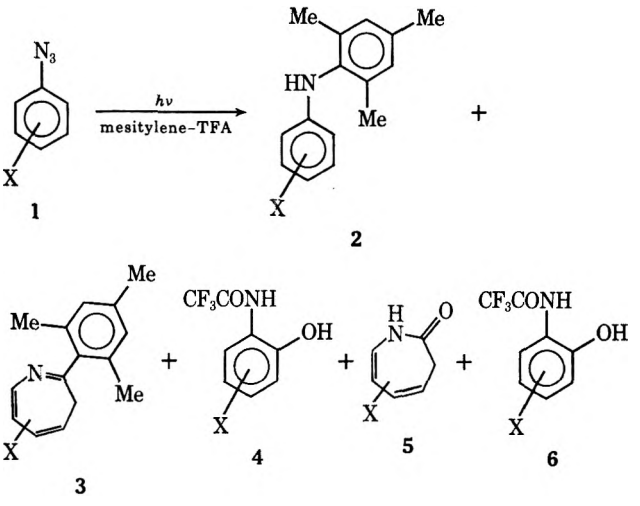

TABLE I
PRODUCT YIELD[a]

		Photochemical reactions					Thermal reactions	
Azide	Substituent	2	3	4	5	6	2	4
1a	None	13	10	3	2		55	1
1b	*p*-Me	40		11		2	84	
1c	*o*-Me	39				3	59	
1d	*o*-CF_3	6	6		15		*b*	
1e	*o*-F	36					*b*	
1f	*p*-CO_2Me	48	9	6			*b*	
1g	*o*-MeO	*b*					79	

[a] The yields of products 3–6 varied from run to run presumably because of variable efficiency chromatographic separation. [b] This reaction was not investigated.

Photolysis of phenyl azide in mesitylene containing 7.5% by volume TFA gave two major and two minor

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(4) P. G. Gassman, G. A. Campbell, and R. C. Frederick, *J. Amer. Chem.*, **94**, 3884 (1972).
(5) R. A. Abramovitch, S. R. Challand, and E. F. V. Scriven, *J. Org. Chem.*, **37**, 2705 (1972).

products isolated by chromatography. The major products were 2,4,6-trimethyldiphenylamine (**2a** 13%) and 2-(2,4,6-trimethylphenyl)-3*H*-azepine (**3a**, 10%). The minor products were 2-hydroxytrifluoroacetanilide (**4a**, 3%) and 1,3-dihydro-2*H*-azepin-2-one (**5a**, 2%). Nmr, ir, and mass spectral data permitted assignment of structures to **2a** and **4a**, and the melting points were in agreement with literature values. Compound **3a** was a somewhat unstable oil, but a satisfactory analysis was obtained and the elemental composition was also indicated by mass spectral data. The structure was assigned on the basis of the nmr spectrum. The presence of a mesityl group is indicated by methyl resonances in a 1:2 intensity ratio at δ 2.25 and 2.05 and by a singlet at δ 6.82. The remaining signals are a two-proton doublet, J = 7 Hz, at δ 2.72, a quartet, J = 7 Hz, at 5.13, a two-proton multiplet centered at 6.24 consisting of five principal lines and a doublet at 7.55. The saturated protons at 2.7 require that the phenyl ring has been rearranged. The spin–spin coupling pattern is consistent with the proposed 3*H*-azepine structure. The 2*H*-azepinone **5a** was identified on the basis of elemental analysis, mass spectrum, and consonance of the nmr with a literature report.[6]

Photolysis of *p*-tolyl azide in 50:4 mesitylene–TFA followed by chromatography provided three identifiable products. 2,4,4′,6-Tetramethyldiphenylamine (**2b**) was formed in 40% yield and identified by spectral data and elemental analysis. 4-Methyl-2-hydroxytrifluoroacetanilide was formed in 11% yield and a trace of 4-methyltrifluoroacetanilide was isolated. In comparison with the case of phenyl azide the azepines which are the product of ring expansion have disappeared with a significant increase in the amount of the substitution product **2b**. When methanol was included in the reaction medium, the yield of **2b** dropped to about 10%, **4b** was formed in 4% yield, and 5-methyl-1,3-dihydro-2*H*-azepin-2-one was formed in 8% yield on the basis of quantitative gas chromatographic analysis. The nmr spectrum shows a singlet for the methyl group at δ 1.89 and there is a two-proton doublet at δ 2.80 which was shown by decoupling to be coupled to a triplet at 5.31. There is a doublet at δ 5.70 which is coupled to a doublet of doublets at 6.18. The latter signal also is coupled to the NH proton as it collapses to a doublet on addition of D_2O.

When *p*-tolyl azide is photolyzed in 50:4 benzene–TFA, only **4b** (2%) and **6b** (2%) could be identified. The absence of 4-methyldiphenylamine indicates that benzene is too unreactive a substrate to undergo the substitution process.

Photolysis of *o*-tolyl azide in mesitylene–TFA (50:4) followed by chromatographic work-up gave 2,2′,4,6-tetramethyldiphenylamine (**2c**) (39%). The only other identifiable product, which was isolated only occasionally, was 2-methyltrifluoroacetanilide (**6c**). The formation of the diphenylamine was shown to be dependent on the presence of TFA. When TFA was replaced with ethyl trifluoroacetate, the only photolysis product was 2,2′-dimethylazobenzene (29%). The azo compound was also the only identifiable product when the solvent medium was pure mesitylene.

o-Trifluoromethylphenyl azide was also photolyzed in mesitylene–TFA (50:4). The yield of the diphenylamine **2d** was 6%. 3-Trifluoromethyl-1,3-dihydro-2*H*-azepin-2-one (**5d**) was formed in 15% yield. Spectral data for the formation of the 3*H*-azepine **3d**, which is analogous to **3a**, were obtained, but the instability of this compound prevented final characterization by analysis.

Photolysis of *o*-fluorophenyl azide under similar conditions gave the diphenylamine **2e** (42%). There was also formed a series of minor products. Although the structural assignments cannot be considered conclusive, the spectral data suggest that the minor products include 2-(2,4,6-trimethylphenyl)-5-hydroxytrifluoroacetanilide (1–3%), 2-hydroxytrifluoroacetanilide (1.5%), and an oxidative dimer of 2-hydroxytrifluoroacetanilide. All of the latter three products appear to have lost the ring fluorine by processes which are obscure at this time.

Photolysis of *p*-carbomethoxyphenyl azide gave the diphenylamine **2f** in 48% yield. Also formed were **3f** (9% yield) and **4f** (6%). Identification of **2f** and **4f** followed from elemental composition and comparison of spectral properties with those of the analogous compounds previously described. The composition of **3f** was deduced from the precise mass determination of the parent ion in the high-resolution mass spectrum. The ambient temperature nmr was suggestive of the 3*H*-azepine structure since a triplet at 6.35 and a doublet at 7.80 could be assigned to the C-4 and C-7 protons, respectively. However, the signal which could be assigned to the C-3 methylene group was broad and partially overlapped the aromatic methyl groups. The nmr is temperature dependent. The three methyl groups of the mesityl group are all nonequivalent below −30°. This proves that the mesityl is a substituent on a nonplanar ring in agreement with the assigned azepine structure. At 60° the broad signal due to the methylene group appeared as a doublet as expected for the assigned structure.

o-Methoxyphenyl azide decomposed under the reaction conditions at an appreciable rate in the absence of light. Control experiments demonstrated that the other azides did not decompose at rates competitive with photolysis in the absence of irradiation.

Photolyses of phenyl azide and *p*-tolyl azide were also conducted in anisole. In the former case 2-methoxydiphenylamine (**7**, 8%), 4-methoxydiphenylamine (**8**, 18%), and *o*-hydroxytrifluoroacetanilide (4%) were isolated. In the latter case 2-methoxy-4′-methyldiphenylamine (**9**, 4%), 4-methoxy-4′-methyldiphenylamine (**10**, 43%), and 2-hydroxy-4-methyltrifluoroacetanilide (15%) were formed.

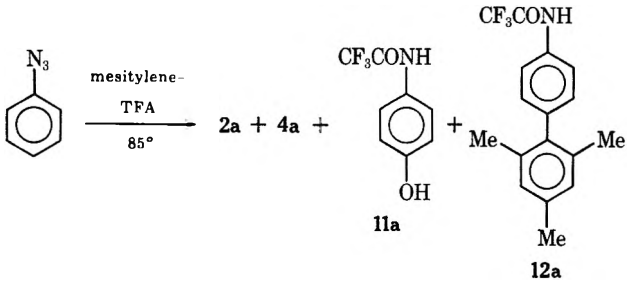
B. Thermal Reactions.—Several of the azides were subjected to thermal decomposition at 85 ± 5° in the same 50:4 mesitylene–TFA medium employed in the photolyses. Under these conditions the yields of diphenylamines increased appreciably and products derived from apparent ring expansion of a nitrene intermediate were not observed. The reactions are considered individually in the succeeding paragraphs.

Phenyl azide gave the diphenylamine **1a** in 55% yield. Small amounts of *2*-hydroxytrifluoroacetanilide (1%) and the 4-hydroxy isomer (4%) were isolated. The only other product which could be characterized after chromatographic work-up was a compound as-

(6) E. Vogel, R. Erb, G. Lenz, and A. A. Bothner-By, *Justus Liebigs Ann. Chem.*, **682**, 1 (1965).

signed the biphenyl structure **12a** (5%) as shown in Scheme II. The elemental composition was deduced

SCHEME II



from the low-resolution mass spectrum and analysis. The nmr spectrum strongly indicated a para-substituted aromatic ring and a mesityl group.

The thermal decomposition of *p*-tolyl azide in mesitylene–TFA was quite clean. The only product isolated was the diphenylamine **2b** (84%). The reaction of *o*-tolyl azide gave **2c** in 59% yield along with the 2-methyl compound **12c** (2%) analogous to **12a**. *p*-Carbomethoxyphenyl azide remained largely unreacted (>85% recovery) after 24 hr at 85° in 50:4 mesitylene–TFA. A small amount of diphenylamine **2f** was the only reaction product detected. *o*-Methoxyphenyl azide evolved nitrogen at room temperature in 50:4 mesitylene–TFA with evolution of 57% of the theoretical amount of nitrogen after 3.5 hr. Product isolation after 48 hr gave the diphenylamine **2g** (79%) and a small amount of what is apparently a dehydro dimer (2%).

The scope of these acid-catalyzed thermal reactions with respect to the aromatic solvent–substrate was investigated using *p*-tolyl azide. In addition to the case of mesitylene, the expected diphenylamines were isolated from reactions in *p*-xylene [2,4′,5-trimethyldiphenylamine (**13**, 66%)], anisole [2-methoxy-4′-methyldiphenylamine (**9**, 4%), 4-methoxy-4′-methyldiphenylamine (**10**, 62%)], and toluene [2,4′-dimethyldiphenylamine (**14**, 5%), 4,4′-dimethyldiphenylamine (**15**, 26%)]. No tractable products were found after reaction in 50:4 benzene–TFA for 24 hr at reflux, although azide decomposition was complete.

The rate of decomposition of *p*-tolyl azide measured by gas evolution at 80° in a 25:4 mixture of aromatic solvent and TFA was strongly dependent on the aromatic solvent. Pseudo-first-order rate constants of 1.5×10^{-1} and 7.6×10^{-3} min^{-1} were measured for mesitylene and anisole, respectively. In acetophenone nitrogen evolution was <15% complete in 10 hr, making estimation of a rate unreliable but demonstrating that the reaction is very slow in this case.

Discussion

The common pattern of reactivity which is found in both the photochemical and thermal reactions is the formation of diarylamines. This reaction exhibits features which distinguish it from two other general mechanisms which operate in the decomposition of aryl azides. Unimolecular thermal decomposition to the nitrene gives diphenylamines, probably by an addition–ring opening sequence,[7,8] but only when the azide is substituted by electron-withdrawing groups.[5] This limitation has been attributed to the reduced electrophilicity of the nitrene intermediate in the absence of such substituents.[5] From the point of view of scope, then, the present acid-catalyzed thermal decomposition is complementary with respect to the azides to which it can be applied. As in the nitrene process, the aromatic substrate must be more reactive than benzene to give significant yields of diphenylamines.

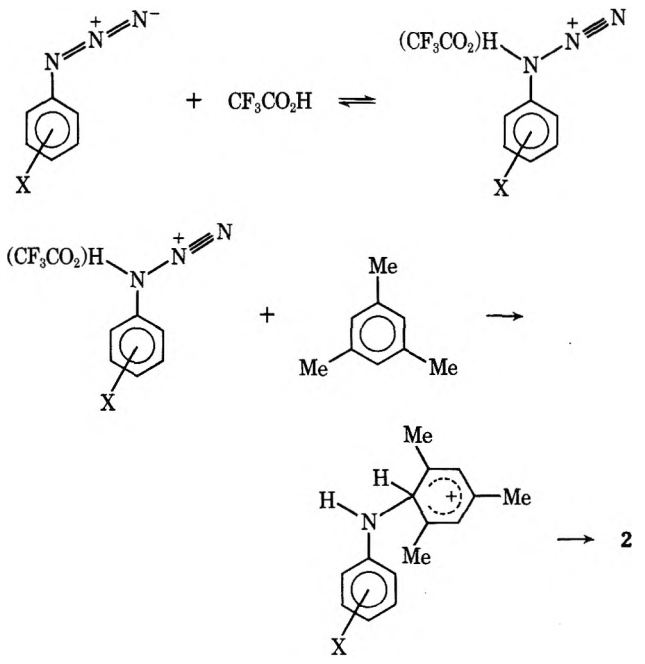
Decomposition of the azide under the present conditions might *a priori* have been expected to occur *via* a nitrenium ion as is proposed, for example, for certain decompositions of azides in strong acids.[9,10] Two features of our results argue against this reaction being dominant under our conditions. The strong dependence of the rate on the identity of the solvent is inconsistent with rate-determining unimolecular decomposition of the conjugate acid of the azide, as required for a mechanism involving a discrete nitrenium ion. Furthermore, the site of electrophilic attack is at nitrogen, not the ortho and para positions of the ring. It is these sites which are the primary points of nucleophilic attack in reactions which are believed to involve aryl nitrenium ions.[2,4]

The general mechanistic features of the thermal reactions can be summarized as follows. The reaction is acid catalyzed and, since the rate is strongly influenced by the solvent–substrate, the aromatic substrate is apparently involved in the rate-determining step. The reaction is facilitated by electron-releasing substituents and retarded by electron-withdrawing groups on the aryl azide as illustrated in particular by the *p*-methoxy and *p*-carbomethoxy cases. The structures of the products demonstrate that the primary electrophilic site is at the nitrogen atom of the aryl azide. Only relatively reactive aromatic rings are suitable substrates for substitution. We propose the mechanism of Scheme III to account for these features of the reaction.

The mechanism of Scheme III is analogous to that proposed by Smith and Brown[11] for decomposition of biphenyl azides in HBr–acetic acid. In that case evidence was obtained for formation of *N*-bromoanilines as intermediates resulting from nucleophilic attack of bromide on the conjugate acid of the azide. The reaction is probably also related mechanistically to the aluminum trichloride catalyzed decomposition of aryl azides which also gives diphenylamines when conduced in aromatic solvents.[12] It may also be related to formation of cyclopropanes from the TFA-catalyzed decomposition of phenyldiazomethane in olefins.[13] A hydrogen-bonded complex of TFA and phenyldiazomethane was proposed as the reactive species in that reaction.

(7) R. J. Sundberg and R. H. Smith, Jr., *Tetrahedron Lett.*, 267 (1971).
(8) R. A. Abramovitch, S. R. Challand, and E. F. V. Scriven, *J. Amer. Chem. Soc.*, **94**, 1374 (1972).
(9) R. A. Abramovitch and E. P. Kyba in "The Chemistry of the Azido Group," S. Patai, Ed., Interscience, New York, N. Y., 1971, pp 234–241.
(10) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," W. A. Benjamin, Inc., New York, N. Y., 1966, pp 225, 226; J. H. Boyer and F. C. Canter, *Chem. Rev.*, **54**, 1 (1954).
(11) P. A. S. Smith and B. B. Brown, *J. Amer. Chem. Soc.*, **73**, 2438 (1951).
(12) W. Borsche and H. Hahn, *Chem. Ber.*, **82**, 260 (1949).
(13) G. L. Closs, R. A. Moss, and S. H. Goh, *J. Amer. Chem. Soc.*, **88**, 364 (1966).

SCHEME III

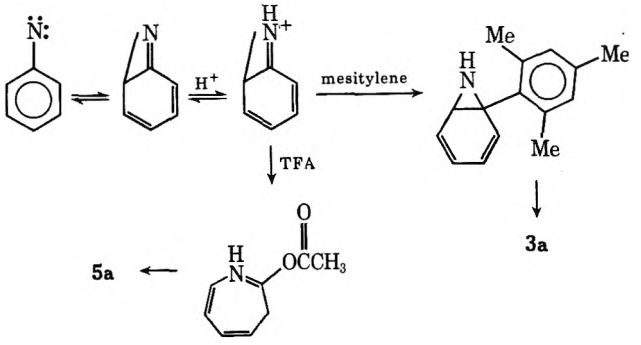


The mechanism of Scheme III is intended to convey primarily the conclusion that the observed electrophilic substitution does not involve a nitrene intermediate. The data indicating that the aromatic substrate is involved in the rate-determining step also argue against a discrete nitrenium ion. The electrophile would, therefore, appear to be a protonated (or hydrogen bonded) aryl azide molecule which is capable of attacking reactive aromatic substrates at a rate exceeding unimolecular elimination of nitrogen.

The case of phenyl azide indicates that the nitrenium ion pathway may be a competitive process. The production of the hydroxyacetanilides **4a** and **11a** is suggestive of a nitrenium ion intermediate. The formation of the biphenyl **12a** can also be accounted for in this way. The isolation of **12c** from thermal decomposition of *o*-tolyl azide also suggests a small amount of the nitrenium ion pathway in this case. No evidence of formation of nitrenium ion products was found for either *p*-tolyl or *o*-methoxy azide.

The photolytic processes appear to involve at least two competitive reaction systems. Products having rearranged aromatic skeletons as found in products **3** and **5** are highly suggestive of aryl nitrene intermediates.[7] The diphenylamines which are formed, however, cannot be reasonably accounted for in terms of a nitrene intermediate. Nucleophilic trapping of unrearranged aryl nitrenes has been observed only rarely and only when the aryl nitrene bears electron-withdrawing substituents.[14] Under the present conditions electron-donating methyl groups clearly do not prevent diphenylamine formation. An aryl nitrenium ion formed by protonation of an aryl nitrene is not a satisfactory intermediate. Substantial amounts of ortho and para substitution products, for example **12**, or formation of methoxy derivatives in the presence of methanol would be expected if aryl nitrenium ions were involved. Instead the most satisfactory explanation would seem to view the photochemical decompositions as involving competition between the nitrene rearrangement pathway and the mechanism of Scheme III. Since control experiments have indicated that the reaction is too rapid to be a purely thermal process, there must exist a photochemical mechanism for generating protonated azide molecules having sufficient energy for the substitution process to occur. Photoexcited azide molecules may be intercepted by protonation prior to complete thermal equilibration, or protonation of excited azides followed by rapid reaction with the aromatic substrates may be involved.

The formation of azepine **3a** represents a new type of reactivity for phenylnitrene. Formally, the product is analogous to the 2-diethylamino-3*H*-azepines formed when phenylnitrene is generated in the presence of secondary amines.[15] However, the effective trapping of phenylnitrene is restricted to good nucleophiles such as amines and hydrogen sulfide.[15b] Furthermore **3a** is not formed in the absence of trifluoroacetic acid so a proton donor is apparently required. We have no evidence for the mechanism of formation of **3a** beyond the analogy with nucleophilic trapping and the dependence on a proton source. A process such as shown below can be written to account for the product structure but, of course, has no significance beyond this at the



present time. The azepinone **5a** can be accounted for by the reaction of trifluoroacetate ion with rearranged phenylnitrene, followed by deacylation. Only **4a** is suggestive of the involvement of an aryl nitrenium ion and the absence of the 4 isomer argues against the presence of a free aryl nitrenium ion capable of attack by nucleophiles at both the ortho and para position. This surmise is strengthened by results of a photolysis of phenyl azide in 40:10:4 mesitylene–methanol–TFA. No *o*- or *p*-anisidine was detected. The products were **5a** (14%) and **4a** (trace). The increased amounts of azepinones found in the presence of methanol suggest that some of the azepinone might arise *via* a methoxyazepine.

The electrophilic substitution process described in this work considerably expands the possibilities for synthesis of unsymmetrical diphenylamines *via* aryl azides relative to prior procedures.[5] Although the mechanism by which this reaction occurs is not established in detail, there is considerable evidence that protonated aryl azide or a hydrogen-bonded complex of the azide with TFA can act as the electrophilic species by a process which bypasses a free nitrene or nitrenium ion intermediate.

(14) R. A. Odum and A. M. Aaronson, *J. Amer. Chem. Soc.*, **91**, 5680 (1969); R. Huisgen and K. V. Fraunberg, *Tetrahedron Lett.*, 2595 (1969).

(15) (a) R. J. Sundberg, S. R. Suter, and M. Brenner, *J. Amer. Chem. Soc.*, **94**, 513 (1972), and references therein; (b) W. von E. Doering and R. A. Odum, *Tetrahedron*, **22**, 81 (1966).

Experimental Section[16]

Photolytic Reactions.—A weighed amount of the azide (~10 mmol) was dissolved in mesitylene (50 ml) and trifluoroacetic acid (4 ml) was added. The resulting solution was purged with nitrogen for 0.5 hr and then irradiated for 3.0 hr by a 450-W Hanovia mercury lamp using a Pyrex filter and a water-cooled Vycor immersion well. The temperature in the reaction solution did not exceed 30° under these conditions. At the completion of photolysis the reaction mixture was diluted with ether (100 ml) and washed thoroughly with sodium bicarbonate solution to remove trifluoroacetic acid. The residue from evaporation of the ether and mesitylene was chromatographed on a column of silica gel (70–230 mesh). The products from the individual azides are described below in order of their elution from the column.

Phenyl Azide.—Hexane–ether (95:5) readily eluted 2,4,6-trimethyldiphenylamine (**2a**) (13%, glpc 16%): mp 56.5–57° (lit.[17] mp 54°), after recrystallization from hexane; nmr (CCl_4) δ 2.16 (s, 6), 2.30 (s, 3), 5.1 (broad s, 1), 6.4–7.4 (m, 7); mass spectrum 212 (25), 211 (100), 210 (46), 196 (45), 194 (27), 181 (19), 180 (17), 167 (6), 134 (21), 91 (21), 77 (17), 65 (6). Hexane–ether (90:10) eluted 2-(2,4,6-trimethylphenyl)-3*H*-azepine (**3a**) (10%, glpc yield 11.5%) as an oil: nmr (CCl_4) δ 2.05 (s, 6), 2.25 (s, 3), 2.9–2.6 (broad d, J = 7 Hz, 2), 5.15 (q, 1), 6.65–6.1 (m, 2), 6.82 (s, 2), 7.55 (d, 1, J = 7 Hz); mass spectrum 212 (23), 211 (100), 210 (46), 196 (58), 181 (25), 167 (8), 146 (19), 134 (135), 130 (16), 92 (21), 76 (17), 65 (29). Hexane–ether (50:50) eluted 2-hydroxytrifluoroacetanilide (**4a**): 3%; mp 164.5–165° (lit.[18] mp 167–169°), after recrystallization from carbon tetrachloride; mass spectrum 206 (9), 205 (79), 187 (10), 137 (15), 136 (100), (58), 80 (71). Ether eluted 1,3-dihydro-2*H*-azepin-2-one (**5a**) (2% by glpc) (purification was effected by preparative glpc using an SE-30 column at 180°, and the nmr spectrum was in accord with a reported spectrum):[6] mass spectrum 110 (7.5), 109 (83), 81 (32), 80 (100), 66 (23), 53 (28).

When the photolysis was carried out in 40:10:4 mesitylene–methanol–TFA, the only products isolated by a similar work-up procedure were **5a** (14%) and **4a** (trace).

When the photolysis was carried out in 50:4 anisole–TFA, the products isolated were 2-methoxydiphenylamine (**7**, 8%), 4-methoxydiphenylamine (**8**, 18%), and *o*-hydroxytrifluoroacetanilide (4%), each of which was identified by spectral comparison with purified samples from other reactions.

***p*-Tolyl Azide.**—The products isolated by the standard work-up and chromatographic separation are listed in order of elution. Hexane–ether (95:5) eluted 2,4,4′,6-tetramethyldiphenylamine (40%): mp 66–67°, after recrystallization from hexane; nmr (CCl_4) δ 2.08 (s, 6), 2.16 (s, 3), 2.22 (s, 3), 4.8 (broad s, 1), 6.3 (d, 2, J = 7 Hz), 6.8 (s overlapping d, J = 7 Hz, 4); mass spectrum 226 (19), 225 (100), 224 (25), 210 (24), 209 (9), 208 (16), 195 (10.5), 194 (9), 193 (6), 134 (7.5). Hexane–ether (90:10) eluted 4-methyltrifluoroacetanilide, 2%, mp 109–110, after recrystallization from hexane (lit.[19] mp 112–113°), having expected spectral properties. Hexane–ether (80:20) eluted 2-hydroxy-4-methyltrifluoroacetanilide (11%): mp 193–194°, after recrystallization from chloroform; nmr (acetone-d_6) δ 2.27 (s, 3), 6.6–6.8 (s at 6.8 overlapping d, J = 8 Hz at 6.7, 2), 7.7 (d, 1, J = 8 Hz), 8.9 (broad, 2); mass spectrum 220 (14), 219 (90), 201 (14), 200 (14), 151 (14), 150 (100), 123 (14), 122 (65), 94 (60), 78 (28), 77 (34).

When the photolysis was carried out in 40:10:4 mesitylene–methanol–TFA, **2b** was isolated in 10% yield and **4b** in 4% yield. Acetone eluted a crude fraction containing azepinone **5b** in 8% yield based on glpc. The analytical sample was collected as an oil by preparative glpc using an SE-30 column at 175°: nmr ($CDCl_3$) 1.89 (s, 3), 2.80 (d, 2, J = 7 Hz), 5.33 (broad t, 1, J = 7 Hz), 5.80 (d, J = 9 Hz), 6.18 (d of d, J = 9, 4 Hz), 8.8 (very broad, 1). Spin decoupling established that the signals at 2.80 and 5.33 were coupled. Deuterium exchange established that the 4-Hz coupling present in the signal at 6.18 is with N–H. Mass spectrum 124: (14.5), 123 (100), 108 (16), 95 (25), 94 (100), 70 (67), 44 (98).

When the photolysis was carried out in 50:4 benzene–TFA, 4-methyltrifluoroacetanilide (2%) and **4b** (3%) were the only products isolated.

When the photolysis was carried out in 50:4 anisole–TFA, the products were 2-methoxy-4′-methyldiphenylamine (**9**, 4% by glpc), 4-methoxy-4′-methyldiphenylamine (**10**, 43%, isolated), and 2-hydroxy-4-methyltrifluoroacetanilide (15%).

***o*-Tolyl Azide.**—Hexane–ether (95:5) eluted 2,2′,4,6-tetramethyldiphenylamine (39%): mp 78.5–79.5° after recrystallization from petroleum ether; nmr (CCl_4) δ 2.12 (s, 6), 2.28 (s, 6), 4.7 (broad s, 1), 6.02 (d, 1, J = 8 Hz), 6.80 (s, 2), 6.4–7.0 (m, 3); mass spectrum 226 (21), 225 (100), 224 (11), 210 (25), 209 (10), 208 (20), 195 (15), 194 (13), 134 (10), 121 (18).

In some runs a small amount (~3%) of 2-methyltrifluoroacetanilide, mp 79–80° (lit.[19] mp 81–82°), was isolated and identified by spectral properties.

When the photolysis was conducted in 50:4 mesitylene–ethyl trifluoroacetate, no **2c** was formed. The only product isolated was 2,2′-dimethylazobenzene (29%), mp 53–55° (lit.[20] mp 55°), identified by spectral properties.

***o*-Trifluoromethylphenyl Azide.**—Hexane–ether (98:2) eluted 2,4,6-trimethyl-2′-trifluoromethyldiphenylamine **2d** (6%): mp 66–69°, after preparative glpc on a 5% SE-30 column at 160°; nmr (CCl_4) δ 2.17 (s, 6), 2.33 (s, 3), 5.65 (broad s, 1) 6.21 (d, 1, J = 8 Hz), 6.4–7.2 (m, with s at 6.94, 4), 7.45 (d, 1, J = 7 Hz); mass spectrum 279 (100), 265 (9.5), 244 (62), 230 (9.5), 225 (14), 211 (12), 209 (14), 195 (9.5), 182 (7), 170 (7), 134 (20), 132 (12), 120 (12), 92 (28), 70 (57). Hexane–ether (90:10) eluted an oil with spectral properties suggesting that it was mainly 2-mesityl-3-trifluoromethyl-3*H*-azepine (**3d**): nmr ($CDCl_3$) 4.2 (d, J = 5 Hz), 5.38 (d of d, J = 5, 9 Hz), 6.2–7.0 (m), 7.62 (d, J = 8 Hz). Completely pure samples that would permit conclusive identification or analysis were not obtained. Ether eluted 3-trifluoromethyl-1,3-dihydro-2*H*-azepin-2-one (**5d**): 15% yield; mp 138–138.5°, after recrystallization from carbon tetrachloride; nmr (acetone-d_6) δ 3.4 (d of d, 1, J = 6, 1 Hz), 5.55 (d of d, 1, J = 9, 4 Hz), 5.90 (d of d, J = 9, 4 Hz), 6.65 (m, 2); mass spectrum 178 (13), 177 (100), 158 (46), 149 (17), 148 (15), 129 (25), 128 (25), 121 (19), 119 (60), 117 (69), 108 (81), 102 (25), 101 (23), 84 (33), 82 (92), 80 (100), 53 (42), 39 (23).

2-Fluorophenyl Azide.—Hexane–ether (95:5) eluted **2e**: 36% yield; mp 80–81°, after recrystallization from hexane; nmr (CCl_4) δ 2.17 (s, 6), 2.29 (s, 3), 5.1 (broad s, 1), 6.0–7.0 (m, 6–7); mass spectrum 230 (31), 229 (100), 228 (23), 114 (29), 112 (17), 108 (33), 194 (17), 134 (19), 121 (15), 120 (8). Hexane–ether (80:20) eluted a fraction containing 2-(mesityl)-5-hydroxytrifluoroacetanilide. The pure compound[15] (1% yield) was obtained by recrystallization from carbon tetrachloride: mp 192–192.5°; nmr (acetone-d_6) δ 2.05 (s, 6), 2.30 (s, 3) 3.2 (s, 1, OH?) 6.7–7.0 (m, 3), 7.1 (d, 1, J = 8 Hz), 7.70 (d, 1, J = 1.5 Hz), 9.3 (broad s, 1, NH); mass spectrum 324 (20), 323 (100), 322 (5), 290 (5), 254 (17), 226 (25), 210 (15), 195 (10).

Hexane–ether (50:50) eluted a fraction containing 2-hydroxytrifluoroacetanilide (1%), mp 163–164°, identified by spectral comparison with an authentic sample.

The photolyzed solution in this case contained a substantial amount of insoluble precipitate. The only substance which could be isolated in pure form[15] (2% yield) from this solid appeared to be a dehydro dimer of 2-hydroxytrifluoroacetanilide: mp >290°; nmr (DMSO-d_6) δ 7.0 (d, J = 7 Hz), 7.38 (d, J = 7 Hz), 7.52 (s), 10.0 (broad s), 10.5 (broad s); mass spectrum 409 (21), 408 (100), 390 (14), 372 (14), 339 (25), 321 (12), 311 (62), 293 (19), 171 (43), 149 (71).

***p*-Carbomethoxyphenyl Azide.**—Benzene–ether (90:10) eluted a mixture which was primarily the diphenylamine **2f** but also contained two other components according to tlc. The mixture was dissolved in hexane and refrigerated giving crystalline **2f**: 40% yield; mp 116–118°, after repeated recrystallization from hexane; nmr ($CDCl_3$) δ 2.18 (s, 6), 2.32 (s, 3), 3.84 (s, 3), 5.60 (broad s, 1), 6.41 (d, J = 9 Hz, 2) 6.93 (s, 2), 7.80 (d, J = 9 Hz, 2). The mother liquors from this crystallization contained additional **2f** (8%, total yield 48%) and two other materials. One was separated by preparative tlc on alumina (5:4:1 hexane–benzene–ether) and identified as unreacted **1f** (~15% recovery). The third material was extracted by 8% hydrochloric acid and isolated by basification and extraction to give **3f** (9% yield) (final purification was accomplished by preparative layer chromatog-

(16) Satisfactory analytical values (±0.4% for C, H, and N) were reported for compound **2b–2g**, **3a**, **4b**, **4f**, **5b**, **5d**, **9**, **10**, **12a**, and **12c**, and other compounds as noted: Ed.

(17) C. Izard-Verchère and C. Viel, *Bull. Soc. Chim. Fr.*, 2122 (1971).

(18) M. Pailer and W. J. Huebsch, *Monatsh. Chem.*, **97**, 1541 (1966).

(19) K. G. Rutherford, S. Y.-S. Ing, and R. J. Thibert, *Can. J. Chem.*, **43**, 541 (1965).

(20) I. Heibron, "Dictionary of Organic Compounds," 4th ed, Oxford University Press, London, 1965, p 1145.

raphy on alumina: nmr peaks ($CDCl_3$) δ 2.05 (s, 6; resolved at −50° to two s at 1.7 and 2.5), 2.18 (s, 3), 2.80 (very broad, 2, sharpened to doublet at 60°), 3.81 (s, 3), 6.19 (t, 1), 6.7–7.0 (m, 3), 7.65 (d, 1); mass spectrum 269 (100), 255 (22), 254 (52), 238 (15), 211 (52), 210 (89), 196 (18), 195 (26), 194 (18), 146 (30), 145 (18), 130 (26), 124 (48), 109 (40), 91 (30), 79 (26), 78 (26), 77 (22); accurate mass determination P^+ 269.1398 (calcd 269.1416). Benzene–ether (80:20) eluted **4f** (6%): mp 217–218°, after recrystallization from chloroform–hexane; nmr (acetone-d_6) δ 3.45 (s, 3), 7.0–7.3 (s overlapping d, 2), 7.68 (d, J = 8 Hz, 1); mass spectrum 263 (60), 233 (60), 214 (10), 194 (100), 176 (22), 166 (31), 162 (20), 148 (18), 147 (4), 146 (2), 145 (5), 144 (5), 110 (7), 109 (2), 108 (4), 107 (8), 106 (13), 79 (22), 78 (21), 69 (23), 54 (17), 53 (26), 52 (22), 51 (10).

Thermal Reactions.—A weighed amount of the azide (~10 mmol) was dissolved in the appropriate aromatic substrate (50 ml) and trifluoroacetic acid (4 ml) was added. The reaction flask was equipped with a condenser, and a nitrogen atmosphere was established. The flask was wrapped to prevent any competing photochemical reactions and heated at steam bath temperature (85 ± 5°) for 12–24 hr. Rate measurements subsequently established that the heating period could be shortened for azides with electron-donor substituents. The reaction mixture was then cooled and diluted with 100 ml of ether, washed thoroughly with sodium bicarbonate solution, dried, and concentrated to remove ether and the aromatic solvent. The residue was then subjected to column chromatography using silica gel.

Phenyl Azide.—Reaction was carried out in 50:4 mesitylene–TFA for 16 hr. A crystalline compound separated on removal of the mesitylene from the reaction mixture. This was identified by spectral data as 4-hydroxytrifluoroacetanilide (4%), mp 173–174° (lit.[18] mp 172–173°). On chromatography of the remainder of the product, hexane–ether (95:5) eluted **2a** (55%), identified by spectral comparison with the compound isolated from the photochemical reaction. This was followed by 2,4,6-trimethyl-4′-trifluoroacetamidobiphenyl (**12a**, 5%): mp 113–115°, after recrystallization from hexane; nmr ($CDCl_3$) δ 2.12 (s, 6), 2.29 (s, 3), 5.85 (broad s, 1) 6.42 (d, J = 9 Hz, 2), 6.90 (s, 2), 7.80 (d, J = 9 Hz, 2); mass spectrum 307 (45), 238 (90), 210 (5), 209 (5), 208 (8), 195 (20), 119 (12), 91 (4). Benzene–hexane–ether (2:2:1) eluted *o*-hydroxytrifluoroacetanilide (1%), identified by spectral comparison with a previously prepared sample.

Reaction in 50:4 anisole–TFA gave, on elution of the column with 95:5 hexane–ether, first 2-methoxydiphenylamine (4%) identified by spectral data and then 4-methoxydiphenylamine (6%), mp 104–106° (lit.[21] mp 105°).

***p*-Tolyl Azide.**—Reaction in 50:4 mesitylene-TFA for 12 hr followed by chromatography gave 2,4,4′,6-tetramethyldiphenylamine (84%) having spectral properties identical with the sample prepared in the photochemical reaction.

Reaction in 50:4 *p*-xylene-TFA for 12 hr gave 2,4′,5-trimethyldiphenylamine (9): 66% yield; mp 49.5–50.5° (lit.[17] mp 51°), after recrystallization from hexane; nmr ($CDCl_3$) δ 2.18, 2.22, 2.28 (closely spaced singlets, 9), 5.18 (broad s, 1), 6.65 (d, J = 8, 2), 6.8–7.2 (m, 5).

Reaction in 50:4 toluene–TFA for 24 hr followed by chromatography gave a mixture of 2,4′-dimethyldiphenylamine (**14**) and 4,4′-dimethyldiphenylamine (**15**). Crystallization from hexane gave **15** (19%), mp 79° (lit.[22] mp 78–79°). The mother liquors contained **14** (5%) and additional **15** (7%), as determined by glpc.

Reaction in 50:4 benzene–TFA gave a large amount of intractable tarry precipitate, and no 4-methyldiphenylamine was found.

Reaction in 50:4 anisole–TFA for 12 hr followed by chromatography gave, on elution with 95:5 hexane–ether, 2-methoxy-4′-methylbiphenylamine (**12**, 6%), an oil purified by bulb-to-bulb distillation: nmr ($CDCl_3$) δ 2.28 (s, 3), 3.83 (s, 3), 5.9 (very broad s, 1), 6.8–7.3 (m, 8); mass spectrum 213 (100), 198 (**45**), 197 (33), 196 (17), 183 (90), 155 (11), 154 (8), 91 (14), 77 (**14**), 65 (17). There was also obtained 4-methoxy-4′-methyldiphenylamine (**13**): 62% yield; mp 82–83°,[23] after recrystallization from hexane; nmr ($CDCl_3$) δ 2.25 (s, 3), 3.75 (s, 3), 5.35 (broad s, 1), 6.6–7.1 (m, 8); mass spectrum 213 (91), 198 (100) 155 (10), 154 (14), 128 (9), 91 (15), 65 (19).

***o*-Tolyl Azide.**—Reaction in 50:4 mesitylene–TFA for 2 hr gave **2c** (59% yield), identified by spectral comparison with the sample prepared photolytically. Hexane–ether (90:10) eluted 4′-trifluoroacetamido-2,3′,4,6-tetramethylbiphenyl (**12c**): 2% yield; mp 135–137°, after recrystallization from hexane; nmr ($CDCl_3$) δ 2.15 (s, 6), 2.35 (overlapping s, 6), 5.60 (broad s, 1), 6.1 (d, J = 8 Hz, 1), 6.95 (s, 2), 7.6–7.9 (m, 2); mass spectrum 321 (63), 252 (100), 222 (5), 209 (16), 208 (16), 111 (7), 104 (7), 104 (7).

***p*-Carbomethoxyphenyl Azide.**—After 24 hr at 85° in 50:4 mesitylene–TFA, 85% of the azide was recovered unreacted. The only product isolated by chromatography was 4′-carbomethoxy-2,4,6-trimethyldiphenylamine (**2f**, 20% yield based on unrecovered azide).

***o*-Methoxyphenyl Azide.**—The reaction in 50:4 mesitylene–TFA was carried out at room temperatures for 48 hr. Hexane–ether (90:10) eluted the diphenylamine **2g**: 79% yield; mp 100–100.5, after recrystallization from hexane; nmr (CCl_4) δ 2.14 (s, 6), 2.26 (s, 3), 3.87 (s, 3), 5.35 (broad s, 1), 6.0 (m, 1), 6.5–6.8 (m, 3), 6.82 (s, 3), 6.82 (s, 2); mass spectrum 242 (30), 241 (100), 226 (28), 211 (23), 210 (79), 209 (37), 208 (15), 207 (32). There was also obtained a compound which is apparently the dehydro dimer *N*,*N*′-bis(2,4,6-trimethylphenyl)-2,2′-dimethoxybenzidine:[16] 2% yield; mp 255–257°, after recrystallization from acetone; nmr ($CDCl_3$) δ 2.20 (s, 12), 2.13 (s, 6), 4.00 (s, 6), 5.60 (broad s, 2), 6.18 (d, J = 8 Hz, 2), 6.8–7.1 (m, 8); mass spectrum 481 (38), 480 (100).

Rates of Decomposition of *p*-Tolyl Azide.—A solution of containing about 1.5 mmol of *p*-tolyl azide in 25 ml of the appropriate solvent was thermostated at 80° in a reaction vessel equipped with a sealed magnetically driven high speed stirrer. The reaction was initiated by addition of TFA (4.0 ml). The rate of the reaction was measured by following nitrogen evolution. The following values were obtained: mesitylene, $k = 1.5 \times 10^{-1}$ min^{-1}, $t_{1/2}$ = 4.6 min; anisole, $k = 7.6 \times 10^{-3}$ min^{-1}, $t_{1/2}$ = 91 min; acetophenone, <15% theoretical N_2 evolution in 10 hr, too slow to measure with accuracy.

Registry No.—**1a**, 622-37-7; **1b**, 2101-86-2; **1c**, 18523-45-0; **1d**, 1548-68-1; **1e**, 3296-04-6; **1f**, 20442-96-0; **1g**, 20442-97-1; **2a**, 23592-67-8; **2b**, 39267-44-2; **2c**, 39267-45-3; **2d**, 39267-46-4; **2e**, 39267-47-5; **2f**, 39267-48-6; **2g**, 39267-49-7; **3a**, 39514-14-2; **3d**, 39267-50-0; **3f**, 39267-51-1; **4a**, 10595-66-1; **4f**, 39267-53-3; **5a**, 2183-86-0; **5b**, 39267-55-5; **5d**, 39267-56-6; **9**, 34160-15-1; **12a**, 39267-58-8; **12b**, 39267-59-9; **12c**, 39267-60-2; **13**, 39253-43-5; 2-hydroxy-4-methyltrifluoroacetanilide, 39267-61-3; 2-hydroxytrifluoroacetanilide, 10595-66-1; *N*,*N*′-bis(2,4,6-trimethylphenyl)-2,2′-dimethoxybenzidine, 39267-63-5.

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(21) A. Dornow and K. Bruncken, *Chem. Ber.*, **82**, 121 (1949).

(22) B. G. H. Daniels, F. T. Naylor, and B. C. Saunders, *J. Chem. Soc.*, 3433 (1951).

(23) This value is not in agreement with a recorded value of 55°: A. B. Sen and A. K. Sen Gupta, *J. Indian Chem. Soc.*, **34**, 413 (1957). However, these authors also record mp 79° for 4-methoxydiphenylamine while other sources agree on mp 105° for 4-methoxydiphenylamine.[21,24,25]

(24) K. C. Kshatriya, S. R. Patel, and K. S. Nargund, *J. Univ. Bombay, Sect. A*, **15**, 42 (1946); *Chem. Abstr.*, **41**, 6214 (1947).

(25) L. G. Makarova, *Izv. Akad. Nauk* SSSR, *Otd. Khim. Nauk*, 741 (1951); *Chem. Abstr.*, **46**, 7532 (1952)

Thermolysis of Trimethylamine-β-carboxypropionimide and Its Derivatives

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Thermolysis of trimethylamine-β-carboxypropionimide gave carbon dioxide, water, formaldehyde, trimethylamine, methanol, ammonium bicarbonate, 1-methylene-2,2-dimethylhydrazine, methyl succinate, *N*-methylsuccinimide, and *N*-dimethylaminosuccinimide. The sodium salt in the same reaction gave polymeric material. The methyl ester gave trimethylamine, methanol, methyl acrylate, trimer of methyl isocyanate, methyl β-carbomethoxyaminopropionate, methyl β-succinimidopropionate, *N*-dimethylaminosuccinimide, and 1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine. The *N*-phenyl- and *N*-ethylamides gave mainly the corresponding 1,2,3,4,5,6-hexahydro 3-substituted 2,4-dioxopyrimidines and *N*-substituted succinimides. Reactions schemes are presented for the formation of abnormal products in these reactions.

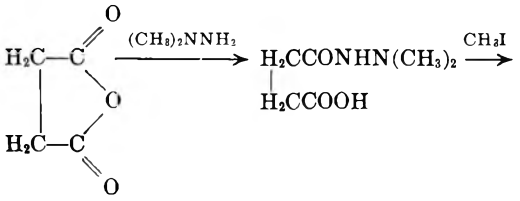
The generation of isocyanato groups in molecules containing an adjacent carboxyl or amide group is useful synthetically for the formation of heterocyclic compounds. 2-Carboxy-3-nitrobenzazide, for example, on heating gave 3-nitroisatoic anhydride.[2] *N*-Methylphthalamide when treated with potassium hypobromite gave 1,2,3,4-tetrahydro-3-methyl-2,4-dioxoquinazoline.[3]

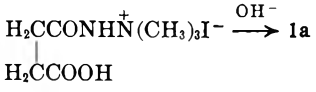
In the present work this type of reaction has been investigated with monoaminimides derived from succinic acid and its derivatives (**1**); aminimides on thermolysis give isocyanates.[4]

$(CH_3)_3\overset{+}{N}\overset{-}{N}COCH_2CH_2COR$

1a, R = ONa
b, R = OH
c, R = OCH_3
d, R = NHC_6H_5
e, R = NHC_2H_5

Sodium trimethylamine-β-carboxylatepropionimide (**1a**) was prepared from succinic anhydride using the following series of reactions.



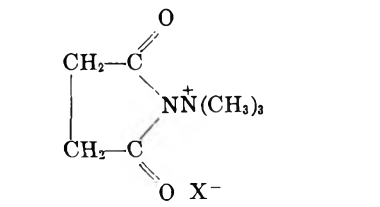


The acid **1b** was prepared from the salt **1a** by the addition of hydrochloric acid. Evidence for the structure of **1b** were infrared absorptions at 1540 cm^{-1} for the aminimide group and 1710 cm^{-1} for the acid. The methyl ester **1c** was synthesized from β-carbomethoxypropionyl chloride using similar reactions to that for the sodium salt **1a**. The amides **1d** and **1e** were prepared by treating the acid **1b** with phenyl isocyanate and ethyl isocyanate, respectively.

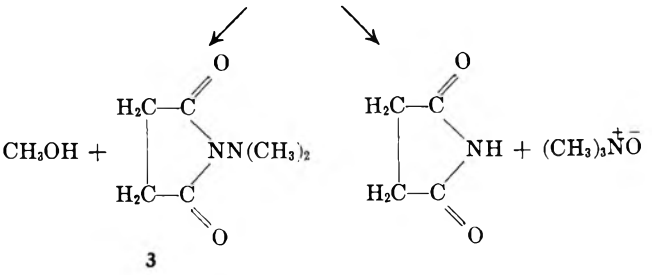
Thermolysis of the sodium salt **1a** neat occurred at a temperature of 250° and proceeded almost explosively. The product was a brittle brown solid which could not be characterized. A similar product was obtained by heating the salt in tetramethylene glycol dimethyl ether.

The thermolysis of the acid **1b** occurred at a lower temperature than that of the salt **1a** and gave the following products: carbon dioxide, water, formaldehyde, trimethylamine, methanol (26.3%), ammonium bicarbonate (3.22%), 1-methylene-2,3-dimethylhydrazine (5.37%), methyl succinate (1.51%), *N*-methylsuccinimide (4.75%), *N*-dimethylaminosuccinimide (49%), methyl β-succimidopropionate (10.4%), and polymeric material.

The formation of *N*-dimethylaminosuccinimide (**3**) in the largest amount suggests that the aminimide **1b** cyclizes during the thermolysis to the quaternary ammonium hydroxide **2a**, which would behave thermally



2a, X^- = OH^-
b, X^- = $^-OOCCH_2CH_2CO\overset{-}{N}\overset{+}{N}(CH_3)_3$
c, X^- = OCH_3^-



like tetramethylammonium hydroxide and form *N*-dimethylaminosuccinimide (**3**), methanol, succinimide, and trimethylamine oxide.

The base **2a** can also react with the aminimide **1b** and form a salt **2b** which thermally can act as a methylating agent similar to other quaternary ammonium salts,[5] and form the methyl ester of the aminimide **1c** and *N*-dimethylaminosuccinimide (**3**). Salts between **2a** and succinimide and trimethylamine oxide in a similar reaction would lead to *N*-methylsuccinimide and the methoxytrimethylammonium ion which is the source of the formaldehyde isolated.[6] The methyl ester of the aminimide **1c** thus formed decomposes normally and forms β-carbomethoxyethyl isocyanate, which can undergo either an elimination reaction with the formation of methyl acrylate and isocyanic acid or hydrolysis

(1) Abstracted in part from the Ph.D. Thesis of J. N. K., June 1973.
(2) T. Curtius and A. Semper, *Ber.*, **46**, 1162 (1913).
(3) F. S. Spring and J. C. Woods, *J. Chem. Soc.*, 625 (1945).
(4) S. Wawzonek and R. C. Gueldner, *J. Org. Chem.*, **30**, 3031 (1965); M. S. Gibson and A. W. Murray, *J. Chem. Soc.*, 880 (1965); R. F. Smith and P. C. Briggs, *Chem. Commun.*, 120 (1965).
(5) A. T. Lawson and N. Collie, *J. Chem. Soc.*, **53**, 624 (1888).
(6) J. Meishenheimer, *Justus Liebigs Ann. Chem.*, **397**, 273 (1913).

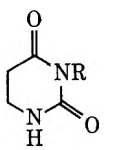
to methyl β-aminopropionate and carbon dioxide. The methyl acrylate thus produced converts a portion of the succimide present to *N*-β-carbomethoxyethylsuccinimide and may be also the basis of the polymer isolated. The isocyanic acid is the precursor of the ammonium bicarbonate isolated.

The source of the small amount of methyl succinate isolated may be the action of base on *N*-dimethylaminosuccinimide (**3**) followed by alkylation *via* **2a**. The yield of 1,1-dimethylhydrazine, the precursor of the methylenedimethylhydrazine isolated, actually is slightly higher (5.31%) than that of methyl succinate (1.51%) and suggests that a portion of the latter may be involved in the formation of *N*-β-carbomethoxyethylsuccinimide.

The thermolysis of **1b** in dimethylformamide gave **3** (52.8%), methyl succinate (5.6%), *N*-methylsuccinimide (5.6%), methyl β-succinimidopropionate (17.6%), and methyl *N*,*N*-dimethylsuccinamate (18.5%). The last compound would be derived from dimethylformamide, since the corresponding acid, for example, can be made from succinic anhydride and dimethylformamide in a 90% yield.[7]

The attempt to confirm the intermediacy of **2a** in the thermolysis of **1b** by synthesis from *N*-dimethylaminosuccinimide (**3**) was not successful. Alkylation of **3** could only be carried out with dimethyl sulfate. Hydrolysis of the salt with barium hydroxide required 3 weeks at steam-bath temperatures and gave a glassy material which upon treatment with hydriodic acid gave trimethylhydrazinium iodide as the only identifiable product.

The decomposition of the methyl ester of the aminimide **1c**, which is extremely hygroscopic, gave products which confirmed its intermediacy in the decomposition of **1b**. The following compounds were isolated: trimethylamine, methanol (11.9%), methyl acrylate (24.8%), trimethyl-*s*-triazine(1*H*,3*H*,5*H*)trione (trimer of methyl isocyanate) (1.3%), methyl β-carbomethoxyaminopropionate (3.6%), methyl β-succinimidopropionate (1.7%), *N*-dimethylaminosuccinimide (**3**) (20.8%), and 1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine (**4a**) (7.1%). Approximately one half of the products can be explained by the thermolysis of the ester **1c** to β-carbomethoxyethyl isocyanate, which can either eliminate isocyanic acid and form acrylate, or react with methanol and give the carbamate.



4a, R = H
b, R = C_6H_5
c, R = C_2H_5

The formation of *N*-dimethylaminosuccinimide (**3**) is indicative of a cyclization reaction of **1c** to a similar intermediate (**2c**) to that formed from the acid **1b**. This intermediate (**2c**) would react with isocyanic acid and form a salt which on thermolysis would give **3**, methanol, and methyl isocyanate. The last compound forms the trimer isolated. Thermolysis of **2c** to succinimide must also occur to a small extent, since the methyl acrylate adduct was formed.

β-Carbomethoxyethyl isocyanate is also the precursor of the pyrimidine. Hydrolysis with traces of water would lead to methyl β-aminopropionate, which after reaction with isocyanic acid would give a urea that would cyclize thermally to **4a**.

The thermolysis of trimethylamine-β-(phenylcarbamoyl)propionimide (**1d**) paralleled that of the ester **1c** and gave *N*-dimethylaminosuccinimide (**3**) (6%), 1,2,3,4,5,6-hexahydro-3-phenyl-2,4-dioxopyrimidine (**4b**) (8.5%), methylaniline (7.1%), aniline (25.7%), and *N*-phenylsuccinimide (29.4%). The first four products would be formed by steps similar to those shown for the ester **1c**. The formation of *N*-phenylsuccinimide must proceed by the displacement of trimethylamine imine from **1d**.

Trimethylamine-β-(ethylcarbamoyl)propionimide (**1e**) in the same reaction gave only 1,2,3,4,5,6-hexahydro-3-ethyl-2,4-dioxopyrimidine (**4c**) (81.6%) and *N*-ethylsuccinimide (14.1%).

Experimental Section[8]

***N*,*N*-Dimethylaminosuccinamic Acid.**—A solution of succinic anhydride (50.2 g) in acetonitrile (300 ml) when treated at its boiling point dropwise with 1,1-dimethylhydrazine (38 g) gave a white, insoluble precipitate. The resulting mixture was refluxed for an additional 0.5 hr, cooled, and filtered. The resulting white solid (63.2 g) upon recrystallization from ethanol melted at 158.5–159.0°: ir (Nujol) 3300 (NH), 3200–2500 (COOH), 1715, 1640 cm^{-1} (CO); nmr (D_2O) δ 2.64 [s, 6, $N(CH_3)_2$] and 2.52 (m, 4, CH_2CH_2).

Anal. Calcd for $C_6H_{12}N_2O_3$: C, 44.99; H, 7.55; N, 17.49. Found: C, 44.69; H, 7.84; N, 17.56.

1,1,1-Trimethyl-2-(β-carboxypropionyl)hydrazinium Iodide.—A solution of *N*-dimethylaminosuccinamic acid (120 g) in a mixture of acetonitrile (550 ml) and water (90 ml) was treated dropwise at its boiling point with methyl iodide (137.0 g). The resulting solution was refluxed for 2 hr and the solvent was removed under reduced pressure. The solid obtained was recrystallized from a mixture of methanol and ether: yield 172 g; mp 137–138.5°; ir (Nujol) 3280 (NH), 3000–2500 (COOH), 1698 cm^{-1} (CO); nmr (D_2O) δ 3.78 [s, 9, $N(CH_3)_3$], 2.70 (s, 4, CH_2-CH_2).

Anal. Calcd for $C_7H_{15}N_2O_3I$: C, 27.83; H, 5.01; N, 9.27. Found: C, 27.71; H, 5.07; N, 9.27.

Sodium Trimethylamine-β-Carboxylatepropionimide (1a).—A solution of the hydrazinium iodide (46.0 g) in water (200 ml) was neutralized with 1 *N* sodium hydroxide. Removal of the water under reduced pressure gave a solid which was mixed with sand and extracted with dry acetone for 2 weeks to remove the sodium iodide. The resulting mixture was dissolved in methanol and filtered. Removal of the methanol gave a solid which was recrystallized from a methanol–ethyl acetate mixture: yield 26.1 g; mp 246° dec; ir (Nujol) 1610–1540 cm^{-1} (CO); mmr (D_2O) δ 3.40 [s, 9, $N(CH_3)_3$], 2.37 (m, 4, CH_2CH_2).

Anal. Calcd for $C_7H_{13}N_2O_3Na$: C, 42.85; H, 6.69; N, 14.28. Found: C, 42.65; H, 6.95; N, 14.32.

Trimethylamine-β-carboxypropionimide (1b).—A solution of the sodium salt (13.27 g) in 50% methanol (100 ml) was treated with 50 ml of 1.3535 *N* hydrochloric acid. Removal of the solvent followed by extraction with hot chloroform gave a solid which was recrystallized from methanol–ether: yield 10.6 g; mp 150.5–151.5° dec; ir (Nujol) 3000–2500 (COOH), 1710, 1540 cm^{-1} (CO); nmr (D_2O) δ 3.48 [s, 9, $N(CH_3)_3$], 2.42 (s, 4, CH_2-CH_2).

Anal. Calcd for $C_7H_{14}N_2O_3$: C, 48.31; H, 8.37; N, 16.23. Found: C, 48.26; H, 8.10; N, 16.08.

(7) G. M. Coppinger, *J. Amer. Chem. Soc.*, **76**, 1372 (1954).

(8) Melting points were corrected; boiling points were not corrected. Infrared spectra were obtained using a Perkin-Elmer 137B infrared spectrophotometer and nmr spectra were recorded with a Varian A-60 nmr spectrometer. Mass spectra were measured using a Hitachi RMU6E mass spectrometer. Gas chromatographic analysis were carried out with a Hewlett-Packard Model 5750B research gas chromatograph.

Pyrolysis of Trimethylamine-β-carboxypropionimide (1b). A. Solid.—The aminimide (0.8 g) was heated in a distilling flask at 180–190° until the evolution of trimethylamine ceased. The volatile products were a liquid and a white solid which was partially soluble in the liquid. The white solid (0.35 g) from its chemical behavior and ir and nmr spectra was identified as ammonium bicarbonate.

The liquid, which gave a positive chromotropic acid test for formaldehyde, was neutralized with hydrochloric acid and the solution was extracted with benzene. Neutralization of the acid extract followed by glc analysis indicated the presence of ammonia, 1,1-dimethylhydrazine, and trimethylamine.

Direct analysis of the original distillate by gas chromatography and nmr indicated the presence of the following compounds: ammonium bicarbonate (0.45 g), water (0.28 g), methanol (1.49 g), and 1-methylene-2,2-dimethylhydrazine (0.55 g).

The residue (20.9 g) from the pyrolysis was dissolved in benzene and filtered from an insoluble solid (3.96 g), and was found on the basis of gas chromatography using a silicone rubber W98 column and tlc on silica to consist of four components. Chromatography using a silica gel column and eluting with benzene and benzene–ethyl acetate (19:1) gave the following compounds: methyl succinate (0.39 g), *N*-methylsuccinimide (0.95 g), *N*-dimethylaminosuccinimide (**3**) (12.2 g), and methyl β-(*N*-succinimido)-propionate (3.4 g). The first three compounds were identified by comparison with authentic samples. The last compound was identical with a sample synthesized from methyl β-aminopropionate.

The residue insoluble in benzene was polymeric in nature and was not investigated further.

B. Solution in Dimethylformamide.—A solution of the aminimide (2.42 g) in dimethylformamide (10 ml) was refluxed until the evolution of trimethylamine ceased. Removal of the dimethylformamide under reduced pressure gave a black, oily residue (1.98 g) which upon the basis of gas chromatographic analysis using a 10% silicone rubber W98 column contained dimethyl succinate (5.6%), *N*-methylsuccinimide (5.6%), *N*,*N*-dimethylaminosuccinimide (**3**) (52.8%), methyl *N*,*N*-dimethylsuccinamate (18.5%), and methyl β-succinimidopropionate (17.6%) in the relative percentages listed. Ammonium bicarbonate (0.3 g) was also isolated as a sublimate in the condenser used in the pyrolysis.

Methyl β-Succinimidopropionate.—A mixture of methyl β-aminopropionate hydrochloride (21.0 g) in benzene (500 ml) was treated at room temperature dropwise with succinyl chloride (23.3 g) and then refluxed for 12 hr. The resulting dark brown solution was filtered and gave upon removal of the benzene and fractional distillation a colorless liquid: bp 143–145° (1 mm); n^{25}D 1.4794; yield 15.6 g; ir (neat) 1775, 1715 (imide), 1760 cm^{-1} ($COOCH_3$); nmr ($CDCl_3$) δ 3.77 (t, 2, NCH_2), 3.66 (s, 3, OCH_3), 2.72 (s, 4, CH_2CH_2), 2.58 (t, 2, CH_2C); mol wt 185 (mass spectrum).

Anal. Calcd for $C_8H_{11}NO_4$: C, 51.89; H, 5.99; N, 7.57. Found: C, 51.78; H, 5.99; N, 7.45.

Methyl *N*,*N*-Dimethylaminosuccinamate Hydrochloride.—*N*,*N*-Dimethylaminosuccinamic acid (40.0 g) was refluxed with a solution of hydrogen chloride (23.0 g) in methanol (400 ml) for 17 hr. Removal of the solvent gave a liquid which separated into two layers. The smaller layer (5.7 g) was dimethyl succinate. The larger layer (44.2 g) was purified by crystallization from methanol–ether and gave white crystals melting at 109.5–11.5°: ir (Nujol) 3420 (NH), 2770 (NH^+), 1750, 1710 cm^{-1} (CO); nmr (D_2O) δ 3.65 (s, 3, CH_3O), 3.20 [s, 6, $NH(CH_3)_2$], 2.65 (s, 4, CH_2CH_2).

Anal. Calcd for $C_7H_{15}N_2O_3Cl$: C, 39.91; H, 7.18; N, 13.30. Found: C, 39.91; H, 7.09; N, 13.21.

Methyl *N*,*N*-Dimethylaminosuccinamate. A.—A suspension of the hydrochloride (17.5 g) in ether (400 ml) was treated with triethylamine (10.1 g). Filtration of the resulting mixture followed by removal of the ether gave a white solid which was recrystallized from benzene–hexane, yield 4.1 g, mp 93–95°.

B.—A solution of β-carbomethoxypropionyl chloride (37.6 g) in ether (200 ml) at 10–20° was treated with a mixture of dimethylhydrazine (16.0 g) and trimethylamine (50 g) in ether (300 ml). The reaction mixture was stirred at room temperature for 4 hr and filtered. The filtrate upon removal of the solvent gave a pale yellow solid (11.0 g). More of this solid was obtained by extracting the precipitate of amine hydrochlorides with three 300-ml portions of ethyl acetate. Recrystallization of the solid from toluene gave white crystals melting at 93–95°: yield 36.2 g; ir (Nujol) 3290, 3190 (NH), 1740, 1680 cm^{-1} (CO); nmr (D_2O) δ 3.75 (s, 3, CH_3O), 2.62 (m, 4, CH_2CH_2), 2.58 [s, 6, $N(CH_3)_2$].

Anal. Calcd for $C_7H_{14}N_2O_3$: C, 48.26; H, 8.10; N, 16.08. Found: C, 47.94; H, 8.26; N, 15.95.

1,1,1-Trimethyl-2-β-carbomethoxypropionylhydrazinium Iodide.—A solution of methyl *N*,*N*-dimethylaminosuccinamate (30.0 g) and methyl iodide (32 g) in acetonitrile (500 ml) was refluxed for 3.5 hr. Removal of the acetonitrile gave a solid which was recrystallized from methanol–ether: yield 49.9 g; mp 132.5–3.5°; ir (Nujol) 3205 (NH), 1735, 1690 cm^{-1} (CO); nmr (D_2O) δ 3.88 [s, 12, $N(CH_3)_3$, CH_3O], 2.83 (m, 4, CH_2CH_2).

Anal. Calcd for $C_8H_{17}N_2O_3I$: C, 30.39; H, 5.42; N, 8.86. Found: C, 30.21; H, 5.38; N, 8.80.

1,1,1-Trimethyl-2-β-carbomethoxypropionylhydrazinium Chloride.—This compound was prepared in a similar fashion to the iodide by heating the ester and methyl chloride in a Paar bomb at 100° for 16 hr. The chloride was recrystallized from methanol–ether and melted at 165.0° dec: yield 82.5%; ir (Nujol) 3010 (NH), 1745, 1695 cm^{-1} (CO); nmr (D_2O) δ 3.77 [s, 9, $N(CH_3)_3$], 3.75 (s, 3, CH_3O), 2.72 (s, 4, CH_2CH_2).

Anal. Calcd for $C_8H_{17}N_2O_3Cl$: C, 42.76; H, 7.62; N, 12.47. Found: C, 42.89; H, 7.87; N, 12.67.

Trimethylamine-β-carbomethoxypropionimide (1c).—A solution of the hydrazinium chloride (44.9 g) in water (100 ml) was neutralized with 1 *N* sodium hydroxide. Removal of the water gave a solid which was extracted with hot ethyl acetate (400 ml). The ethyl acetate solution gave upon evaporation of the solvent a white solid, which upon crystallization from ethyl acetate melted at 114–6.5°; yield 33.1 g; ir (Nujol) 1740 ($COOCH_3$), 1580 cm^{-1} (CON); nmr (D_2O) δ 3.64 (s, 3, CH_3O), 3.39 [s, 9, $N(CH_3)_3$], 2.42 (m, 4, CH_2CH_2).

Anal. Calcd for $C_8H_{16}N_2O_3$: C, 51.05; H, 8.57; N, 14.89. Found: C, 50.68; H, 8.65; N, 14.83.

The hydrazinium iodide in the same reaction gave a mixture of the aminimide and sodium iodide which could only be separated by preparative thin layer chromatography.

Pyrolysis of Trimethylamine-β-carbomethoxypropionimide (1c).—Pyrolysis of the solid aminimide (10.4 g) was carried out in a distillation flask at 190–200°. The liquid collected consisted of trimethylamine (0.09 g), methanol (0.21 g), and methyl acrylate (1.18 g).

A chloroform extract of the residue (4.92 g) in the distilling flask upon separation by chromatography on silica gel using benzene and benzene–ethyl acetate as eluting solvents gave trimethyl-*s*-triazine(1*H*,3*H*,5*H*)trione (1.20 g), mp 174–176° (lit.[9] mp 176°), methyl β-carbomethoxyaminopropionate (0.32 g), mp 29–31° (lit.[10] mp 33.5°), methyl β-succinimidopropionate (0.17 g), *N*-dimethylaminosuccinimide (**3**) (1.63 g), and 1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine (**4a**) (0.45 g), mp 273–277° dec (lit.[11] mp 275°). Identification in all cases was made by comparison with authentic samples.

The remainder of the pyrolysis residue (1.15 g) was a black, viscous oil which was not investigated further.

Trimethylamine-β-phenylcarbamoylpropionimide (1d).—This compound was prepared from trimethylamine-β-carboxypropionimide and phenyl isocyanate in a 48.2% yield by slight modification of the procedure used for the ethyl derivative. The original product obtained was dissolved in water to remove diphenylurea: mp 169–170.5°; ir (Nujol) 3220 (NH), 1680 (CONH), 1550 cm^{-1} (CON); nmr (D_2O) δ 7.22 (m, 5, C_6H_5), 3.18 [s, 9, $N(CH_3)_3$], 2.43 (m, 4, CH_2CH_2).

Anal. Calcd for $C_{13}H_{19}N_3O_2$: C, 62.63; H, 7.68; N, 16.86. Found: C, 62.83; H, 7.68; N, 16.53.

Trimethylamine-β-(ethylcarbamoyl)propionimide (1e).—A solution of trimethylamine-β-carboxypropionimide (20.0 g) and ethyl isocyanate (16.0 g) in chloroform (400 ml) was refluxed for 2.5 hr. Removal of the solvent gave a solid, which was triturated with ether and then refluxed in acetonitrile (50 ml) with decolorizing carbon for 1 hr. Filtration followed by removal of the solvent gave a white solid which was recrystallized from acetonitrile: yield 12.9 g; mp 167.5–169.5°; ir (Nujol) 3360 (NH), 1660 (CONH), 1580 cm^{-1} (CON); nmr ($CDCl_3$) δ 3.40 [s, 9, $N(CH_3)_3$], 3.20 (q, 2, $-CH_2N$), 2.40 (m, 4, CH_2-CH_2), 1.11 (t, 3, CH_3).

(9) A. W. Hofmann, *Ber.*, **19**, 2061 (1880).
(10) F. Lengfeld and J. Stieglitz, *Amer. Chem. J.*, **15**, 215 (1893).
(11) E. Fischer and G. Roeder, *Ber.*, **34**, 3751 (1901).

Anal. Calcd for $C_9H_{19}N_3O_2$: C, 53.71; H, 9.52; N, 20.88. Found: C, 53.97; H, 9.71; N, 21.06.

Pyrolysis of Trimethylamine-β-phenylcarbamoylpropionimide (1d).—Pyrolysis of the aminimide (5.22 g) at 200–220° gave a liquid which distilled and a solid residue. The liquid, based upon chromatographic analysis using a silicone rubber W98 column, consisted of aniline (0.5 g), *N*-methylaniline (0.16 g), and *N*-dimethylaminosuccinimide (**3**) (0.18 g).

The residue upon chromatography using a silica gel column and ethyl acetate as the eluting solvent gave *N*-phenylsuccinimide (1.08 g), mp 152.5–154.5° (lit.[12] mp 155°), and 1,2,3,4,5,6-hexahydro-3-phenyl-2,4-dioxopyrimidine (**4b**) (0.34 g), mp 233.5° (lit.[13] mp 231–234°). Identification was made by comparison with authentic samples.

Pyrolysis of Trimethylamine-β-ethylcarbamoylpropionimide (1e).—Decomposition of the aminimide (5.02 g) at 200–220° gave a dark solid (3.51 g) which upon vacuum sublimation at 120° (16 mm) gave a white solid (3.34 g). Analysis by gas chromatography at 220° using a silicone rubber W98 column showed two compounds in a 12:1 ratio. The first component was identified by its migration as *N*-ethylsuccinimide. The second component was isolated by recrystallizing the mixture from ethanol and was identified as 1,2,3,4,5,6-hexahydro-3-ethyl-2,4-dioxopyrimidine (**4c**) by comparison with a sample synthesized from *N*-ethylsuccinamide, yield 2.89 g, mp 113–114.5°.

1,2,3,4,5,6-Hexahydro-3-ethyl-2,4-dioxopyrimidine (4c).—A solution of *N*-ethylsuccinamide (3.3 g) and lead tetraacetate (10.5 g) in dimethylformamide (30 ml) was heated with stirring at 60–70°. Removal of the dimethylformamide gave a solid which was extracted with ether. Removal of the ether followed by recrystallization from ethanol gave white crystals melting at 113.4–114.5°: yield 0.94 g; ir (Nujol) 3285, 3120 (NH), 1720, 1650 cm^{-1} (CO); nmr ($CDCl_3$) δ 7.32 (s, 1, NH), 3.80 (q, 2, NCH_2CH_3), 3.40 (t, 2, CH_2NH), 2.68 (t, 2, CH_2CO), 1.13 (t, 3, CH_3); mol wt 142 (mass spectrum).

Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.89; H, 7.24; N, 19.92.

***N,N,N*-Trimethyl-*N*-(*N'*-succinimido)ammonium Methyl Sulfate.**—A solution of *N*-dimethylaminosuccinimide (20.0 g) and methyl sulfate (20.2 g) in benzene (400 ml) was refluxed for 24 hr. The solid (12.4 g) formed upon cooling was filtered. The filtrate upon refluxing for an additional 24 hr gave more of the product (16.6 g). Recrystallization of the combined solids from methanol–ether gave white crystals melting at 147.5–149.5°: yield 21.0 g; ir (Nujol) 1895, 1740 (cm^{-1} (CO); nmr (D_2O) δ 4.20 [s, 9, $N(CH_3)_3$], 3.90 (s, 3, CH_3OSO_3), 3.12 (s, 4, CH_2CH_2).

Anal. Calcd for $C_8H_{16}N_2O_6S$: C, 35.81; H, 6.01; N, 10.44. Found: C, 35.80; H, 6.07; N, 10.24.

Reaction of *N,N,N*-Trimethyl-*N*-(*N'*-succinimido)ammonium Methyl Sulfate with Barium Hydroxide.—A solution of the methyl sulfate (5.36 g) and barium hydroxide octahydrate (6.31 g) in water (100 ml) was heated in a sealed flask on a steam bath for 3 weeks. The solution was filtered periodically to remove the barium sulfate. After this period the theoretical amount of barium sulfate was isolated. The resulting solution was saturated with carbon dioxide, filtered, and concentrated to dryness. The resulting product (3.51 g) was a glassy material which was extremely hygroscopic and could not be crystallized. A portion (1.41 g) of this material, when treated in water (50 ml) with 0.0650 *N* hydriodic acid (7.31 ml) gave after removal of the solvent a solid which melted at 229–230° after one recrystallization from methanol, yield 1.1 g. The ir spectrum was identical with that of 1,1,1-trimethylhydrazinium iodide and a mixture melting point was not depressed.

Registry No.—**1a**, 39267-13-5; **1b**, 39267-14-6; **1c**, 39267-15-7; **1d**, 39267-16-8; **1e**, 39267-17-9; **3**, 10574-06-8; **4c**, 39267-19-1; *N,N*-dimethylaminosuccinamic acid, 1596-84-5; succinic anhydride, 108-30-5; 1,1-dimethylhydrazine, 57-14-7; 1,1,1-trimethyl-2-(β-carboxypropionyl)hydrazinium iodide, 39267-21-5; methyl iodide, 74-88-4; methyl β-succinimidopropionate, 39267-22-6; methyl β-aminopropionate hydrochloride, 3196-73-4; succinyl chloride, 543-20-4; methyl *N,N*-dimethylaminosuccinamate hydrochloride, 39267-24-8; methyl *N,N*-dimethylaminosuccinamate, 28402-64-4; β-carbomethoxypropionyl, 1490-25-1; trimethylamine, 75-50-3; 1,1,1-trimethyl-2-β-carbomethoxypropionylhydrazinium iodide, 39267-27-1; 1,1,1-trimethyl-2-β-carbomethoxypropionylhydrazinium chloride, 39477-74-2; methyl chloride, 74-87-3; phenyl isocyanate, 103-71-9; *N*-ethylsuccinimide, 2314-78-5; *N,N,N*-trimethyl-*N*-(*N'*-succinamido)ammonium methyl sulfate, 39267-28-2; barium hydroxide, 12230-71-6; 1,1,1-trimethylhydrazinium iodide, 3288-80-0.

(12) G. Koller, *Ber.*, **37**, 1598 (1904).

(13) S. Hoogewerff and W. A. VanDorp, *Recl. Trav. Chim. Pays-Bas*, **9**, 33 (1890).

3-Substituted Oxetanes

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3-Allyloxyoxetane was rearranged to 3-propenoxyoxetane in 85–90% yield. The *t*-BuOK-catalyzed isomerization was essentially stereospecific, yielding 96% cis isomer. The propenyl ether was cleaved by acid hydrolysis to produce 3-oxetanol in 84% yield. Esterification of oxetanol with tosyl chloride gives crystalline oxetyl tosylate in 90–95% yield. Oxetanone is formed either by mild oxidation of oxetanol with chromic oxide–pyridine complex or by heating oxetyl tosylate in dimethyl sulfoxide. Heating oxetyl tosylate above 150° with alkali halides in triethylene glycol gave 75–85% yields of 3-halo oxetanes as overhead product in about 95% purity. A lower yield (10–20%) of 3-chlorooxetane was obtained when 3-oxetanol was treated with thionyl chloride. Reaction of iodooxetane with diethylamine at 200° gave 3-dimethylaminooxetane. Oxetyl acetate was prepared in 84% yield by transesterification of oxetanol with allyl acetate. Transesterification of oxetanol with ethyl acrylate gave a low yield of oxetyl acrylate; the main product was ethyl 3-(3'-oxetoxy)propionate. The acetate and acrylate esters were also prepared by acylation of oxetanol. Attempts to prepare oxetene by dehydrotosylation of oxetyl tosylate, dehydroacetoxylation of oxetyl acetate, or dehydrohalogenation of chloro- and iodooxetanes were unsuccessful.

The synthesis of 3-allyloxyoxetane[2] afforded an intermediate from which a variety of monosubstituted oxetanes could be prepared.

The work which is presented in this article deals with the isomerization of allyloxyoxetane to propenoxyoxetane followed by cleavage of the propenyl ether to 3-oxetanol[3] and conversion of the latter to halo oxetanes[4] and other new oxetanes.

(1) Address correspondence to this author.

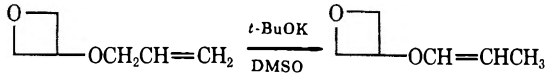
(2) J. A. Wojtowicz, R. J. Polak, and J. A. Zaslowsky, *J. Org. Chem.*, **36**, 2232 (1971).

(3) A. E. Ardis and J. A. Wojtowicz, U. S. Patent 3,446,819 (1969).

(4) S. L. Clark, R. J. Polak, and J. A. Wojtowicz, U. S. Patent 3,517,030 (1970).

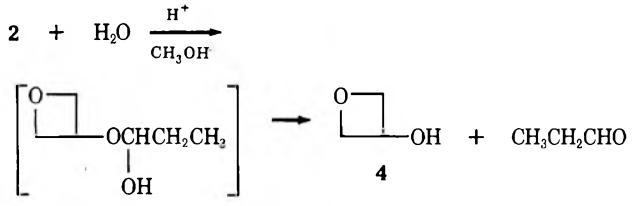
Discussion

Price and Snyder[5] have shown that rearrangement of allyl to propenyl ethers catalyzed by *t*-BuOK in dimethyl sulfoxide is rapid, essentially stereospecific (99% cis isomer), and virtually quantitative. Utilizing this technique, 3-allyloxyoxetane was isomerized to 3-propenoxyoxetane in 85–90% yield. The high conversion (95%) achieved is due to the near-theoretical equilibrium afforded by *t*-BuOK. The product **2** consisted of 96% cis and 4% trans isomer.



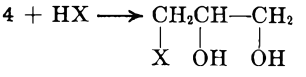
1 **2**

Initial attempts to prepare 3-oxetanol from 3-propenoxyoxetane by cleaving the propenyl ether *via* hydroxylation with alkaline permanganate were not successful owing to attack of the oxetane ring by $KMnO_4$. The propenyl ether, however, was successfully cleaved under mild conditions by acid-catalyzed hydrolysis to 3-oxetanol.



3 **4**

3-Oxetanol readily reacts with anhydrous acids (HCl and HBr), forming 3-halopropanediols in high yields. In contrast, treatment of **4** with anhydrous HF resulted



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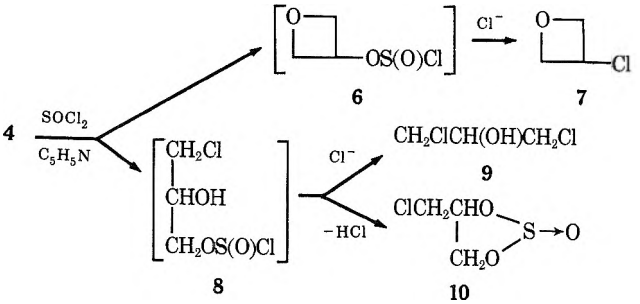
in polymerization. Heating oxetanol in dilute aqueous sulfuric acid gave glycerin in good yield.

Oxetanol slowly polymerizes on standing (under the influence of certain impurities), forming a low molecular weight (1400–1800), white, amorphous solid (mp 125–135°) which is insoluble in monomer. Nmr and infrared examination are consistent with the following structure for the water-soluble polymer: $[-CH_2CH(OH)CH_2O-]_x$.

Treatment of 3-oxetanol with thionyl chloride in pyridine gave low yields of chlorooxetane (10–20%). The main side reaction was ring opening leading to formation of 1,3-dichloropropanol and the cyclic sulfite ester of 3-chloropropanediol. The latter consisted of approximately equal amounts of cis and trans isomers. Products **9** and **10** most probably are formed from **8**;

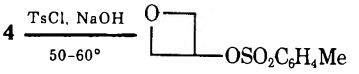


6 **7** **8** **9** **10**

(5) C. C. Price and W. H. Snyder, *J. Amer. Chem. Soc.*, **83**, 1773 (1961).

the latter arises from oxetane ring opening by $SOCl_2$. Reaction of 3-chloropropanediol with $SOCl_2$ in pyridine also gave **10** but no **9**; however, under more vigorous conditions[6] dichloropropanols and trichloropropane can also be formed.

The tosylate route[7] provided a convenient method for preparing halo oxetanes. Oxetyl tosylate yields of 90–95% were consistently obtained by reaction of oxetanol with *p*-toluenesulfonyl chloride (tosyl chloride) in the presence of aqueous sodium hydroxide. Side reactions appear to give small amounts of ring-opening products.



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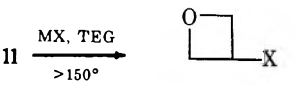
Oxetyl tosylate was converted to 3-halo oxetanes by displacement with alkali metal halides in triethylene glycol (TEG).[8] Yields of 3-halo oxetanes were in the



12, X = F
13, X = Br
14, X = I

range of 60–85%. The data are presented in Table I. The crude products assayed 95% or higher. In the absence of solvent a lower yield (65% compared to 83%) of 3-fluorooxetane was obtained, a higher temperature (200°) was required to initiate reaction, and a much lower reaction rate was observed.

TABLE I
PREPARATION OF HALO OXETANES

X	Oxetyl tosylate, g	Oxetyl tosylate, Mol	Triethylene glycol, ml	Alkali halide, g	Alkali halide, Mol	Halo Oxetane, g	Halo Oxetane, Mol	Yield, %
F	456	2.00	450	465	8.00 (KF)	126	1.66	83[a]
Cl	372	1.63	375[b]	75	1.81 (LiCl)	116	1.25	77
Br	57	0.25	80	36	0.30 (KBr)	20	0.15	60
I	279	1.22	400	220	1.33 (KI)	191	1.04	85

[a] A lower yield of 65% was obtained in the absence of solvent at 200–225°. [b] Using diethylene glycol as solvent the crude product contained dioxane which was extremely difficult to remove by distillation owing to the closeness of its boiling point (101.5°) to that of 3-chlorooxetane (104°).

In the preparation of 3-iodooxetane the main impurities in the crude product were allyl alcohol and iodine. These impurities probably arise from reaction of iodooxetane with HI (from thermal decomposition of iodooxetane) to form 2,3-diiodopropanol, which can thermally decompose. The addition of iodine to allyl alcohol is known to be reversible.[9]

Bigot[10] reportedly prepared "β-epichlorohydrin"

(6) P. B. D. DeLaMare, W. Klyne, D. J. Millan, J. G. Pritchard, and D. Watson, *J. Chem. Soc.*, 1813 (1956).

(7) G. V. D. Tiers, H. A. Brown, and T. S. Reid, *J. Amer. Chem. Soc.*, **75**, 5978 (1953).

(8) An alternate preparation of 3-fluorooxetane which involves dehydrohalogenation of 3-halo-2-fluoropropanols will be discussed in a succeeding publication.

(9) B. P. Caldwell and F. A. Pointkowski, *J. Amer. Chem. Soc.*, **56**, 2086 (1934).

(10) A. Bigot, *Ann. Chim. (Paris)*, **22**, 433 (1891).

(3-chlorooxetane) by treating 3-iodo-2-chloropropanol with base. However, it was subsequently shown[11] that the product isolated by Bigot was in fact 2-chloroallyl alcohol.

The isolation of "β-epiiodohydrin" (3-iodooxetane) from dehydrohalogenation of the isomeric allyl alcohol chloro iodides was also claimed by Bigot. His reported boiling point (172–174°) is much too high. The inertness of his product to aqueous KOH at 100° is suggestive of a vinyl type halogen, as would be present in 2-iodoallyl alcohol. The latter could form from dehydrohalogenation of 2,3-diiodopropanol, a not unexpected by-product in the chloroiodination of allyl alcohol. The iodine analysis reported is correct for the suggested compound.

3-Halo oxetanes, like the isomeric epihalohydrins, are colorless liquids possessing ethereal odors and except for fluorooxetane (which is freely miscible with water) are essentially water insoluble. They possess lower boiling points (owing to the presence of secondary halogen atoms) and higher densities (owing to their compact structure) than the epihalohydrins. The physical properties of the halo oxetanes are given in Table II.

Table II

Physical Properties of Halo Oxetanes[a]

Compd	Bp, °C	d_4 (temp, °C)	$n^{20}D$	Ir bands[e] Oxetane ring[d]	Ir bands[e] C–X stretch
FCHCH$_2$OCH$_2$	67	1.109 (26)	1.3729	10.32	9.22
ClCHCH$_2$OCH$_2$	104	1.197 (25)	1.4418	10.28	15.30
BrCHCH$_2$OCH$_2$	125–126[b]	1.773 (29)	1.4863	10.31	18.30
ICHCH$_2$OCH$_2$	159[c]	2.089 (28)	1.5631	10.32	20.60

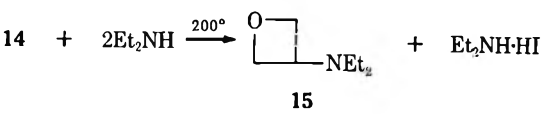
[a] Satisfactory analyses (±0.3% in C, H, and halogen) were obtained for all compounds in the table. [b] 66° (97 Torr). [c] 78° (47 Torr) and 40° (7 Torr). [d] Asymmetric C–O–C stretch. [e] Wavelengths are in microns, ±0.05 μ.

Fluorooxetane was the only halo oxetane which displayed a first-order nmr spectrum. In the case of chlorooxetane the complete five-spin AA'BB'C spectrum (at 90 MHz) occurred within 0.53 ppm. Although resolution was quite good, the spectrum could not be exactly interpreted without computer analysis.

The infrared absorption bands (CH_2 wag, ~8 μ; symmetric and asymmetric C–O–C stretch, ~9.8 and ~10.3 μ; and CH_2 rock, 11–13 μ) of 3-halo oxetanes shift toward higher wavelengths with increasing size of the halogen substituent. 3-Fluorooxetane shows some exceptions to this trend. It also exhibits a strong C–H deformation band at 7.3 μ. This band appears as a very weak absorption at 7.5–7.6 μ in the other halo oxetanes.

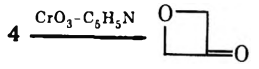
The facile reaction of halo oxetanes with anhydrous acids yields 2,3-dihalopropanols; this is exemplified by the reaction of **7** with HCl to give $CH_2ClCHClCH_2OH$.

Iodooxetane did not react appreciably with diethylamine below 200°. At 200° diethylaminooxetane was obtained in about 20% yield. The low yield is caused by ring opening initiated by the coproduct $Et_2NH \cdot HI$. Reaction of the latter with **15** initially gives $HOCH_2CH(NEt_2)CH_2I$, which reacts further with Et_2NH to form $HOCH_2CH(NEt_2)CH_2NEt_2$. Reaction of **14** with $Et_2NH \cdot HI$ yields $HOCH_2CHICH_2I$, which can react with Et_2NH or thermally decompose to give allyl alcohol and iodine.



15

Mild oxidation of oxetanol with chromic oxide–pyridine[12] complex gave 3-oxetanone in 55% yield.



16

Use of permanganate, dichromate, or Oppenauer oxidation was not successful. Reaction of oxetyl tosylate with dimethyl sulfoxide in the presence of tri-*n*-butylamine gave a 33% yield of oxetanone. The major anticipated product of this reaction, oxetene, was not obtained. Sulfonate esters of secondary alcohols normally yield olefins on heating in dimethyl sulfoxide,[13a] whereas primary tosylates gave high yields of aldehydes.[13b]

Oxetanone exhibits carbonyl absorption at 5.47 μ in the infrared region, indicating a highly strained ring. It is unstable in the presence of base. Oxetanone slowly polymerized on standing, giving a highly viscous material which showed both carbonyl and ether absorption in the infrared and is indicative of polyoxetanone, $[-CH_2C(O)CH_2O-]_x$.

Oxetanone was first prepared[14] (in low yield) by reaction of chloroacetyl chloride with diazomethane followed by treatment with K_2CO_3 and isolation as the dinitrophenylhydrazone, mp 152–155°. Berezin[15] prepared oxetanone (40% yield) by hydroxylation of methyleneoxetane to 3-hydroxymethyl-3-oxetanol followed by cleavage of the glycol. Reduction of **16** in aqueous solution with ruthenium and hydrogen yields **4**.

Although substituted oxetenes have been reported, their structures have not been confirmed. Several attempts were made to prepare the parent compound, oxetene; none were successful. As mentioned earlier, thermal dehydrotosylation of oxetyl tosylate in DMSO did not yield oxetene. Likewise, thermal and chemical dehydroacetoxylation did not lead to oxetene formation. Dehydrohalogenation of chloro and iodo oxetanes gave several products which are indicative of ring fragmentation as well as rearrangement of the desired oxetene (to acrolein).

Dehydration of oxetanol over alumina at 400° gave a crude reaction product which contained water, formaldehyde, acetaldehyde, and acrolein. The latter probably forms by rearrangement of the desired oxetene.

17

(11) W. E. Noland and B. N. Bastian, *J. Amer. Chem. Soc.*, **77**, 3395 (1955).

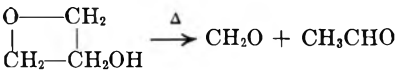
(12) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1958). J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(13) (a) H. R. Nace, *Chem. Ind. (London)*, 1626 (1958); (b) N. Kornblum, W. J. Jones, and G. J. Anderson, *J. Amer. Chem. Soc.*, **81**, 4113 (1959).

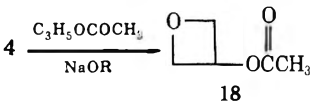
(14) J. R. Marshall and J. Walker, *J. Chem. Soc.*, 467 (1952).

(15) G. H. Berezin, U. S. Patents 3,297,719 (Jan 1967) and 3,449,369 (June 1969).

The formation of formaldehyde and acetaldehyde is indicative of thermolytic ring cleavage.

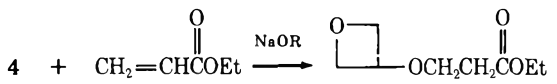


Transesterification of oxetanol with allyl acetate provided oxetyl acetate in 83% yield.



18

Using ethyl acrylate, a low yield (6%) of oxetyl acrylate was obtained. In addition to polymer formation the main by-product (16% yield) was derived from addition of oxetanol to the double bond of ethyl acrylate.



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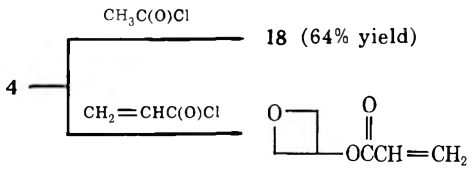
Acylation of oxetanol with acrylyl chloride provided a more satisfactory method for preparing oxetylacrylate; **18** was similarly prepared by treatment of **4** with acetyl chloride in the presence of pyridine.



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Experimental Section

Materials.—3-Allyloxyoxetane was prepared from allyl alcohol and assayed >98%. Other chemicals were commercially available reagent grade.

Analyses.—Gas chromatographic (gc) analyses were conducted using an Aerograph A-90-P manual temperature programmer using 0.25-in. columns. Carrier gas flow was 40 cc/min at 40 psig. Most analyses were carried out using a 5-ft silicone SF-96 column (20% on 80–100 mesh Chromosorb), a 5-ft Igepal column (15% on 80–100 mesh Chromosorb W), or a 3-ft Carbowax 20M Column (5% on 80–100 mesh Chromosorb W). Quantitative analyses were performed using standards of known composition.

Infrared spectra of liquid samples (neat) or solid samples (as Nujol mulls) between salt plates were recorded with a Perkin-Elmer Infracord Model 137. Some spectra were also recorded with a Perkin-Elmer Model 21 spectrometer. Absorption bands due only to the main functional groups in the molecule are given. Complete spectra will be published in the near future by Sadtler.

^1H and ^{19}F nmr spectra were obtained with a Varian A-60 spectrometer. Some proton spectra were also recorded at 90 MHz with a Bruker spectrometer. Tetramethylsilane and $CFCl_3$ were used as internal references.

3-Propenoxyoxetane.—Dimethyl sulfoxide (700 g) and 3-allyloxyoxetane (456 g, 4.0 mol) in a 2-l. three-neck flask were treated (with stirring) with potassium *tert*-butoxide (51 g, 0.46 mol) over a 10-min period. The temperature rose to about 50° after 30 min. Infrared (disappearance of terminal methylene bands at 1.633 and 2.113 μ) and nmr indicated almost complete conversion of allyloxyoxetane. Gc analysis (140°, Igepal column) showed a conversion of 95% as well as the presence of *tert*-butyl alcohol. The latter results from the equilibrium $CH_3S(O)CH_3$ + *t*-BuOK ⇄ $CH_3S(O)CH_2K$ + *t*-BuOH. Filtration followed by distillation through a 24-in. Berl saddles packed column afforded propenoxyoxetane (388 g, 3.4 mol, 85% yield): bp 73–77° (50 mm); d_4^{25} 0.9752; $n^{20}D$ 1.4458; ir 3.27 (cis C–H stretch), 5.97 (C=C), 7.25 and 7.35 (methyl C–H deformation), 8.86 (COC), 10.23 (oxetane ring), and 13.7 μ (cis-propenyl C–H out of plane bending); nmr (60 MHz, $CDCl_3$) (the product is mainly the cis isomer containing about 4% trans isomer)—the propenyl portion of the molecule gave signals at δ_B 1.62 (CH_3), δ_A ~4.5 ppm (=CHC–), and δ_C 5.83 ppm (OCH=); the coupling constants are $J_{AB} \cong 6.5$, $J_{AC} \cong 6.3$, and $J_{BC} \cong 1.7$ Hz; the oxetane ring protons gave a complex uninterpretable multiplet between δ 4.5 and 4.9 ppm. The observed spectrum is actually composed of two five-spin systems (AA'BB'C and A_3MX) which involves over 500 theoretical transitions.

Anal. Calcd for $C_6H_{10}O_2$: C, 63.1; H, 8.83. Found: C, 63.2; H, 8.87.

3-Oxetanol—3-Propenoxyoxetane (136 g, 1.19 mol), water (132 g), methanol (97 g), and 98% H_2SO_4 (0.2 ml) were stirred at room temperature. Methanol was used as cosolvent, since propenoxyoxetane is soluble in water to less than 1% in contrast to allyloxyoxetane, which has a solubility of 15% in water at room temperature. The hydrolysis was conducted at room temperature because of the lability of the oxetane ring in acid media. Under the moderate temperature conditions employed the rate of hydrolysis was quite slow, requiring 5 days to attain 85% conversion (Analysis by gc: 170°, Igepal column). A faster reaction rate could probably be achieved by chemically tying up the propionaldehyde as it formed by means of the oxime or other derivative. The mixture was neutralized with NaOH and stripped in a rotary evaporator at 50° under water aspirator vacuum. The residue was distilled through a 24-in. spinning band column giving 3-oxetanol (62.7 g, 0.85 mol, 84% corrected yield): bp 72–73° (9 mm); d_4^{28} 1.125; $n^{20}D$ 1.4384; ir 2.94 (OH) and 10.36 μ (oxetane ring); nmr (60 MHz, $CDCl_3$) (a first-order spectrum was not obtained)—the oxetane ring protons gave a complex uninterpretable pattern between δ 4.3 and 5.0 ppm, the hydroxyl proton gave a doublet centered at δ 3.37 ppm (J_{HCOH} = 4 Hz).

Anal. Calcd for $C_3H_6O_2$: C, 48.6; H, 8.2. Found: C, 48.5; H, 8.1.

Oxetanol (neat) was treated with anhydrous HCl and HBr at 0°. The pure products were isolated by gc (150–200°, Carbowax column) and identified as 3-chloro-1,2-propanediol and 3-bromo-1,2-propanediol by their ir spectra. Yields were in the neighborhood of 90%.

Oxetanol (1 ml) was refluxed in 1 *N* H_2SO_4 (5 ml) for 30 min. The reaction mixture was neutralized, evaporated, extracted with isopropyl alcohol, and stripped of solvent. Gc and ir showed the product to be about 90% glycerin.

Oxetyl Tosylate.—The reactor was a three-neck, round bottom, 3-l. flask fitted with stirrer, thermometer, and addition funnel. A 20% aqueous caustic solution [NaOH 240 g (6.0 mol), H_2O 1200 ml] was added dropwise to a well-stirred mixture of oxetanol (400 g, 5.40 mol), water (1050 ml), and tosyl chloride (1086 g, 5.70 mol) at 50–55°. Stirring was continued for 1 hr after addition of base; the reaction mixture was neutral to phenolphthalein. After cooling (to room temperature), benzene (1 l.) was added to dissolve the tosylate, the layers were separated, and the aqueous layer was extracted twice with 100 ml of benzene. The combined benzene extracts were washed three times with concentrated NH_4OH to remove unreacted tosyl chloride and then with water to remove NH_4OH. The benzene was removed under vacuum. The solid product was ground with a mortar and pestle and freed of traces of solvent under vacuum. The crude tosylate [1109 g (4.87 mol), 90% yield] melted at 84–87°; after recrystallization from hexane it melted sharply at 88.5–89.0°. The crude product was sufficiently pure for further synthetic work, ir 7.3–7.4 and 8.4–8.5 (SO_2) and10.32 and 10.59 μ (oxetane ring).

Anal. Calcd for $C_{10}H_{12}O_4S$: C, 52.6; H, 5.3; S, 14.1. Found: C, 52.8; H, 5.3; S, 14.1.

3-Fluorooxetane.—Oxetyl tosylate (456 g, 2.00 mol), triethylene glycol (450 ml), and dry KF (465 g, 8.00 mol) were charged into a three-neck, 2-l. flask fitted with stirrer, thermometer, distillation head, and receiver (cooled with Dry Ice). A Dry Ice cooled trap was employed between the receiver and vacuum pump. The system, under reduced pressure (200 Torr), was heated in an oil bath and maintained a 160–170° until the distillation rate was noticeably reduced and then the temperature was slowly raised to 200° to remove the last traces of product. Some difficulty was encountered owing to foaming; this was alleviated by increasing the stirring rate, increasing the pressure slightly, and lowering the temperature or adding more solvent. The product, fluorooxetane [126 (1.66 mol), 83% yield],

was more than 95% pure by gc (100°, silicone column). Redistillation through a 35-cm glass helices packed column gave pure fluorooxetane: bp 67° (760 mm); d_4^{26} 1.109; n^{20}D 1.3729; ir 9.22 (C–F) and 10.32 μ (oxetane ring); nmr ($CDCl_3$) two doublets (four methylene protons) centered at 268 Hz (δ_A 4.65 ppm) and two pentets (one methine proton) centered at 279 Hz (δ_B 5.38 ppm), J_{AB} = 5, J_{AF} = 22.5, and J_{BF} = 56 Hz (from ^{19}F spectrum J_{AF} = 23.6 and J_{BF} = 58 Hz).

Anal. Calcd for C_3H_5OF: C, 47.4; H, 6.63; F, 25.0. Found: C, 47.3; H, 6.59; F, 25.2.

Data on the preparation of other halo oxetanes are given in Table I. The physical properties of halo oxetanes are shown in Table II.

3-Chlorooxetane (from 3-Oxetanol and Thionyl Chloride.)—Thionyl chloride (0.22 ml, 3.0 mmol) was added dropwise to oxetanol (0.20 ml, 3.0 mmol) dissolved in pyridine (0.80 ml). An exothermic reaction occurred, yielding a brown precipitate and a dark brown supernatant liquid. Gc (125°, silicone column) showed complete consumption of oxetanol and the appearance of four new peaks at retention times of 2, 5, 9, and 11 min. Peaks 1 and 2 were identified (after trapping) as 3-chlorooxetane (~15% yield) and 1,3-dichloropropanol by their ir spectra. Peaks 3 and 4 were identified by ir (sulfite 8.35, C–Cl 13.5 μ) and nmr as the cis and trans isomers (~50:50) of the cyclic sulfite ester of 3-chloro-1,2-propanediol. This was substantiated by treating 3-chloro-1,2-propanediol with $SOCl_2$ in pyridine; the cis and trans isomers of the sulfite ester were formed but no dichloropropanol. No chlorooxetane was obtained from oxetanol when dioxane, β-picololine, or tri-*n*-butylamine were substituted for pyridine or with PCl_3 in place of $SOCl_2$. The nmr (90 MHz) spectrum of chlorooxetane in CD_3CN showed a complex region between δ 4.4 and 5.1 ppm.

Treatment of chlorooxetane (neat) at 0° with anhydrous HCl gave 2,3-dichloropropanol in about 90% yield. The product was analyzed by gc and ir.

3-Oxetanone (from 3-Oxetanol).—Oxetanol (11.3 g, 0.153 mol) in methylene chloride (900 g) was treated at 20–25° with freshly prepared $CrO_3 \cdot 2C_5H_5N$ (225 g, 0.88 mol). After 30 min gc (125°, silicone column) showed complete conversion of oxetanol and the appearance of a new peak with a retention time of 1 min. The reaction mixture was filtered and the filtrate was flash distilled to remove dissolved chromium salts. Attempts to dry a portion of the solution with BaO resulted in disappearance of the new peak. Distillation through a 24-in. spinning band still gave a fraction (15.5 g) over the temperature range 88–115°. Gc analysis indicated the presence of mainly pyridine and 39% of the new peak. The latter peak was isolated by preparative gc and identified as 3-oxetanone [6.05 g (0.084 mol), 55% yield] by infrared and nmr: ir 5.47 (C=O) and 10.4 μ (oxetane ring); nmr (60 MHz, $CDCl_3$) singlet at δ 5.40 ppm. Carbonyl analysis using $NH_2OH \cdot HCl$ indicated a purity of >96%. Purified product had micro boiling point (Emich) 106°, d_4^{27} 1.137, and n^{25}D 1.4224. Redistillation through a 24-in. annular still (Nester-Faust) gave pure product.

Anal. Calcd for $C_3H_4O_2$: C, 50.0; H, 5.6. Found: C, 49.8; H, 5.6.

Polymerization of oxetanone occurred during storage at ambient temperature, giving a highly viscous material which showed infrared bands at 5.8 (C=O) and 9.0–9.5 μ (COC).

Oppenauer oxidation of 3-oxetanol did not yield 3-oxetanone. Acetone, cyclohexanone, quinone, anisaldehyde, and cinnamaldehyde were employed as hydrogen acceptors in conjunction with aluminum isopropoxide in benzene and xylene as solvents. Although acetone was obtained as overhead product, only trace quantities of oxetanone were observed by ir and gc.

3-Oxetanone (from Oxetyl Tosylate).—Oxetyl tosylate (3.7 g, 16 mmol), DMSO (10 ml), and tri-*n*-butylamine (5 ml) were heated to reflux in a 25-ml flask attached to a 6-in. Vigreux column and distillation head. A total of 2.7 g of foul-smelling distillate was obtained over a 30-min period. Gc (80°, silicone column) showed six components which were trapped and identified by mass spectral and ir analysis. The weight per cent composition was as follows: CH_3SH, 23%; CH_3SCH_3, 30%; butyraldehyde, 24%; 3-oxetanone, 14% (5.3 mmol, 33% yield); unknown, 2.5%; and CH_3SSCH_3, 7%. The butyraldehyde (9.0 mmol) may arise from oxidative decomposition of n-Bu_3N or by rearrangement and decomposition of the ionic intermediate

$$\overline{CH_2OCH_2CHO\overset{+}{S}}(CH_3)_2$$

Further work is needed to ascertain the origin of butyraldehyde.

3-Diethylaminooxetane.—3-Iodooxetane (5 ml, 57 mmol) and diethylamine (25 ml) were heated in a 100-ml Fischer–Porter aerosol compatibility tube for 1 hr at 200°. Extraction with petroleum ether (bp 30–60°) followed by filtration and atmospheric distillation (maximum temperature: flask 141°, head 62°), gave 9.6 g of a dark brown, crystalline solid and 6.7 g of liquid. Gc (150°, Carbowax column) and ir showed the presence of allyl alcohol (15.5 mmol), unreacted iodooxetane (3.8 mmol), a high boiler, and an intermediate peak with a slight amine-like odor which was identified as 3-diethylaminooxetane. Distillation through a 24-in. spinning band still gave diethylaminooxetane [1.61 g (12.5 mmol), 23% yield], bp 54° (5 mm), and 2.46 g of a higher boiling fraction, bp 60–65° (0.2 mm). Diethylaminooxetane showed ir bands at 7.25 (CH_3) and 10.25 μ (oxetane ring). A chromatographic cut had d_4^{26} 0.900, n^{20}D 1.4427, and neut equiv 127 (calculated 129). In the nmr (60 MHz, $CDCl_3$) four signals were observed in the ratio 3:2:1:4, δ_D 0.98 (CH_3, triplet), δ_C 2.48 (NCH_2, quartet, J_{CD} = 6.9 Hz), δ_B 3.82 (ring CH, second-order splitting observed), and δ_A 4.58 ppm (ring CH_2 groups, doublet, splitting 6.5 Hz).

Anal. Calcd for $C_7H_{15}ON$: C, 65.1; H, 11.7; N, 10.8. Found: C, 65.0; H, 11.6; N, 10.6.

The crystalline solid was recrystallized from benzene, mp 170–172°. It was identified as $(C_2H_5)_2NH \cdot HI$ by comparison of its ir spectrum with that of an authentic sample.

Anal. Calcd for $C_4H_{12}NI$: I, 62.2. Found: 62.0.

2,3-(Diethylamino)propanol.—The high-boiling fraction obtained in the distillation of diethylaminooxetane was identified by ir and nmr as 2,3-(diethylamino)propanol. Gc showed the fraction to be 76% pure [1.87 g (9.3 mmol), 17% yield]. A sample purified by preparative gc had d_4^{26} 0.877 and n^{20}D 1.4510; ir 2.91 (OH) and 7.22 μ (CH_3); nmr (60 MHz, $CDCl_3$) four signals were observed in the ratio 12:11:2:1, 1.03 (triplet, CH_3–), 2.2–3.2 (complex multiplet, NCH– and NCH_2–), 3.5–3.8 (complex multiplet, CH_2O), and 4.85 ppm (broad singlet, hydroxyl). After treatment with a chemical shift complexing reagent, $Eu[CF_3CH_2CF_2C(O)CHC(O)CH(CH_2)_3]_3$, the following spectrum was obtained: four signals were observed in the ratio 12:10:1:2, 1.21 and 1.29 (two triplets, CH_3–), 2.4–3.3 (complex multiplet, NCH_2), 3.87 (pentet, methine proton), and 4.86 ppm (doublet, OCH_2).

Anal. Calcd for $C_{11}H_{26}N_2O$: C, 65.29; H, 12.95; N, 13.85. Found: C, 65.48; H, 12.78; N, 13.68.

Dehydrochlorination of 3-Chlorooxetane.—Chlorooxetane (5.5 g, 58 mmol), powdered NaOH (4.6 g, 116 mmol), and diisobutylcarbinol (20.5 g) were heated to reflux in a 50-ml flask fitted with thermometer, 6-in. glass helices packed column, and distillation head. Six grams of distillate was obtained over the temperature range 80–110°. Gc (135°, Igepal column) and ir showed the presence of chlorooxetane (major) and small amounts of ethanol, propanol, and allyl alcohol as well as solvent.

Dehydroiodination of 3-Iodooxetane.—Sodium (5.8 g, 0.25 g-atom) was dissolved in 2,6,8-trimethyl-4-nonanol (140 g). The solution was cooled to 57° and iodooxetane (46 g, 0.75 mol) was added dropwise. The reaction mixture was distilled under reduced pressure; 34 g of distillate was obtained over the temperature range of 29 (35 Torr) to 72° (8 Torr). Gc (135°, Igepal column) and ir analysis showed the presence of ethanol, acrolein, propanol, unreacted iodooxetane, and some solvent.

Catalytic Dehydration of 3-Oxetanol over Alumina.—Oxetanol (5.5 g, 74 mmol) was added dropwise into a glass tubular reactor packed with Harshaw alumina (No. A1-0104, $^3/_{16}$ in.) and heated to 400° in a tube furnace. At a pressure of 100 Torr and a residence time of 0.5 to 1.0 sec, 3.3 g of starting material was collected in the ice trap and 1.7 g of reaction products was collected in the Dry Ice trap. Gc (70°, silicone column) and ir analysis of the reaction products showed the presence of water, formaldehyde, acetaldehyde, and acrolein.

Oxetyl Acetate.—3-Oxetanol (25.0 g, 0.338 mol), metallic sodium (0.4 g), and allyl acetate (200 ml) were heated to reflux in a 300-ml flask fitted with a 12-in. packed column and distillation head. Distillate (containing allyl alcohol) was slowly taken off while more allyl acetate was added to maintain a constant level in the flask. When the conversion had reached about 60% (gc analysis, 125°, silicone column) the excess allyl acetate was distilled and the residue was vacuum distilled, giving oxetyl acetate (18 g, 0.155 mol) and oxetanol (11 g, 0.15 mol). Corrected yield of oxetyl acetate was 83%; bp 76° (29 mm);

d_4^{30} 1.123 and $n^{20}D$ 1.4241; ir 5.73 (C=O), 8.13 (=COC), and 10.31 (oxetane ring).

Anal. Calcd for $C_5H_8O_3$: C, 51.7; H, 7.81. Found: C, 51.6; H, 7.92.

Oxetyl acetate was also prepared by acylation of oxetanol with acetyl chloride. Oxetanol (5.63 g, 76 mmol) in benzene (75 ml) containing Et_3N (7.70 g, 76 mmol) was treated at 0° with acetyl chloride (5.96 g, 76 mmol). After 30 min gc showed a conversion of 95%. The reaction mixture was extracted with 75 ml of water and the organic phase was washed three times with 10-ml portions of water. Analysis of the water extract after 2 days showed the presence of product, which was extracted with three 15-ml portions of benzene after saturation with salt. Some product was probably lost through hydrolysis in the aqueous phase. The combined organic layers were distilled at atmospheric pressure to remove solvent and the crude product was vacuum distilled through a 6-in. glass helices packed column to give oxetyl acetate (5.33 g, 46 mmol, 64% corrected yield), bp 46–47° (7 mm).

Oxetyl Acrylate.—3-Oxetanol (50.0 g, 0.68 mol), ethyl acrylate (134 g), aluminum isopropoxide (1.5 g), and phenyl-β-naphthylamine (3 g) were heated to reflux. Only a trace of ethanol was found in the distillate. Metallic sodium, (0.5 g) was added, and 100 ml of ethyl acrylate was distilled and replaced with 100 ml of allyl acrylate. The latter was slowly distilled and the residue was vacuum distilled, giving 3-oxetanol (34 g, 0.46 mol), a higher boiler [74–76° (1 Torr), 6 g], and 12 g of pot residue. The oxetanol fraction contained about 5% of a higher boiling material which was trapped by gc (125°, silicone column) and identified as oxetyl acrylate (6% yield) by ir.

Oxetyl acrylate was also prepared by reaction of oxetanol with acrylyl chloride. Oxetanol (5.63 g, 76 mmol) in benzene (75 ml) containing Et_3N (7.70 g, 76 mmol) was treated at 0° with acrylyl chloride (6.88 g, 76 mmol). Conversion after 30 min as determined by gc was about 95%. The reaction mixture was worked up as described under the preparation of oxetyl acetate. The distilled oxetyl acrylate [3.5 g, (27 mmol), 38% corrected yield] had the following physical properties: bp 58° (6.5 mm); d_4^{23} 1.111; $n^{20}D$ 1.4515; ir 5.81 (C=O), 6.13 and 6.18 (C=C), and 10.31 μ (oxetane ring).

Anal. Calcd for $C_6H_8O_3$: C, 56.2; H, 6.29. Found: C, 56.1; H, 6.14.

Ethyl 3-(3′-Oxetoxy)propionate.—The high-boiling fraction obtained in the preparation of oxetyl acrylate was identified by nmr as ethyl 3-(3′-oxetoxy)propionate (0.035 mol, 16% yield): d_4^{21} 1.090; $n^{21}D$ 1.4384; ir 5.77 (C=O), 8.45 (=COC), and 10.29 μ (oxetane ring).

Anal. Calcd for $C_8H_{14}O_4$: C, 55.2; H, 8.10. Found: C, 55.1; H, 8.03.

Attempted Dehydroacetoxylation of Oxetyl Acetate.—In the first experiment oxetyl acetate (9.3 g, 0.08 mol) was passed in 7 min through a 30 × 1 cm Vycor tube at 490 ± 10°. Almost all of the oxetyl acetate was recovered unchanged. In a second run oxetyl acetate (8.1 g, 0.07 mol) was passed in 40 min through the reactor at 605 ± 5°. The condensate was collected in pyridine (14 g) cooled to −40°. This receiver was followed by a water condenser and a −78° trap. The condensate in the first receiver amounted to 6.3 g; nothing was collected in the −78° trap. Gc (Igepal column) and ir showed a small amount of H_2O and unchanged starting material.

Oxetyl acetate was heated in a sealed tube with excess diethylamine for several hours at 150°; no evidence of reaction was observed.

Polyoxetanol.—A freshly distilled sample of 3-oxetanol (about 150 g) became hazy after several weeks under ambient conditions and after a few months it had a milky appearance. Filtration and ether washing gave 0.6 g of white, amorphous powder, mp 125–130°, mol wt (osmometric), 1397. The milky filtrate was distilled (65°, 5 Torr) and the pot residue was dissolved in hot ethanol. On cooling an additional 1.5 g of precipitated polyoxetanol was obtained, mp 125–135°, mol wt, 1723. Both fractions of polyoxetanol were water soluble, ir (KBr) 2.97 (OH) and 8.99 μ (COC), nmr (DMSO-d_6) doublet centered at 4.66 ppm (sec OH).

Anal. Calcd for $(C_3H_6O_2)_x$: C, 48.6; H, 8.16. Found: C, 47.8; H, 8.2.

Registry No.—**1**, 6777-00-0; *cis*-**2**, 40307-01-5; *trans*-**2**, 40307-02-6; **4**, 7748-36-9; **4** polymer, 39275-61-1; **11**, 26272-83-3; **12**, 26272-86-6; **13**, 39267-79-3; **14**, 26272-85-5; **15**, 39267-81-7; **16**, 6704-31-0; **18**, 39267-83-9; **19**, 39267-84-0; **20**, 39267-85-1; tosyl chloride, 98-59-9; diethylamine hydriodide, 19833-78-4; 2,3-(diethylamino)propanol, 13429-30-6; 3-chlorooxetane, 4741-80-4; allyl acetate, 591-87-7; acetyl chloride, 75-36-5; ethyl acrylate, 140-88-5; acrylyl chloride, 814-68-6.

Acknowledgment.—The authors are indebted to Dr. R. C. Rittner, Mr. J. Culmo, and Mr. J. Giunta for microanalyses, and to Mr. G. D. Vickers and Dr. T. Groom for nmr analyses.

On the Mechanism of Alkaline Hydrolysis of Methylthiopurines[1]

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Di- and trimethylthiopurines, which can form anions, are resistant to alkaline hydrolysis. After introduction of an *N*-methyl substituent, these compounds are incapable of forming anions and become susceptible to attack by hydroxyl ion. The course of these reactions can be predicted satisfactorily by Fukui's superdelocalizabilities for nucleophilic attack; the same order of reactivities is derived for analogous methylthio- and chloropurines, in accordance with the limited experimental observations.

Many attempts have been made to establish the order of reactivity of purines toward nucleophilic reagents. The most useful model is 2,6,8-trichloropurine (TCP), in which nucleophilic displacement of the halogens by a variety of bases follows the order 6 > 2 > 8.[2-4] However, for 7- and 9-methyl-TCP, the relative reactivity toward ethoxide ion was found to be 8 > 6 > 2.[4,5] The latter result is in good agreement with the observations of Barlin[6] on the three isomeric 9-methylmonochloropurines and has been explained as follows.[5] The reaction of TCP with bases involves the anion of the substrate, in which the negative charge is concentrated mainly in the imidazole ring, thus making nucleophilic attack at C-8 difficult. The 7- or 9-methyl derivatives of TCP cannot form anions and thus follow the order of reactivity derived

(1) Dedicated to our teacher and friend, Professor E. Lederer, Director, Institut de Chimie des Substances Naturelles, Gif-Sur-Yvette, France, on the occasion of his 65th birthday.

(2) (a) E. Fischer, *Chem. Ber.*, **30**, 2226 (1897); (b) R. K. Robins and B. E. Christensen, *J. Amer. Chem. Soc.*, **74**, 3624 (1952).

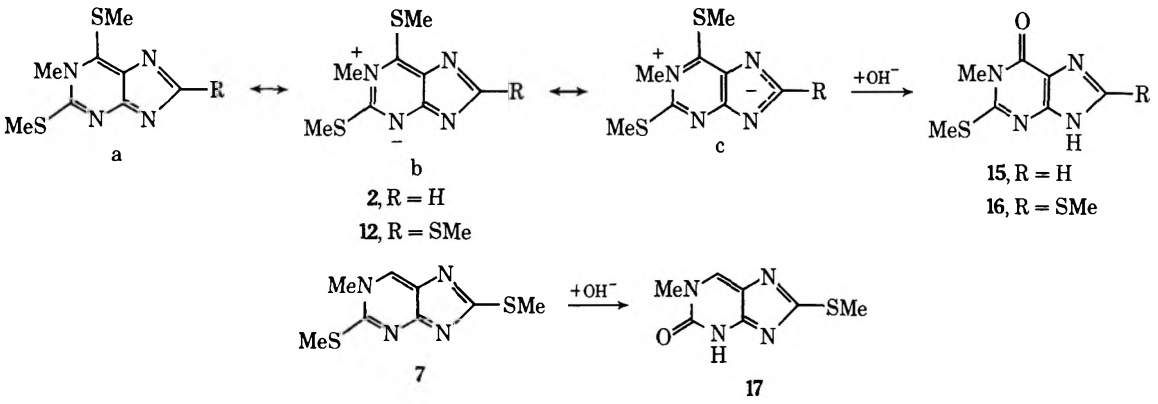
(3) S. R. Breshears, S. S. Wang, S. G. Bechtolt, and B. E. Christensen, *J. Amer. Chem. Soc.*, **81**, 3789 (1959).

(4) E. Fischer, *Chem. Ber.*, **30**, 1846 (1897).

(5) E. Y. Sutcliffe and R. K. Robins, *J. Org. Chem.*, **28**, 1662 (1963).

(6) G. B. Barlin, *J. Chem. Soc. B*, 954 (1967).

SCHEME I



by Mason[7] from MO calculations for the neutral form of purine.

We have reinvestigated this problem, using as a model the alkaline hydrolysis of di- and trimethylthiopurines. We shall demonstrate that the introduction of an *N*-methyl substituent has a decisive influence on the direction of nucleophilic attack, and shall derive a general scheme for these reactions.

The 2,6- (1), 2,8- (6), and 6,8-dimethylthiopurines (8) and likewise the trimethylthio derivative 11 proved to be resistant to hydrolysis by boiling 2 *N* sodium hydroxide. On the other hand, the corresponding 2,6-,[3] 6,8-,[8] and 2,8-dichloropurines,[9] like TCP, do react under these conditions. This we ascribe to the fact that chloride ion is a much better leaving group than the methylmercaptide ion.

In contrast, all *N*-methyl derivatives of the above methylthiopurines, being unable to form anions, undergo alkaline hydrolysis. The results are summarized in Table I.

TABLE I
HYDROLYSIS OF DI- AND TRIMETHYLTHIOPURINES BY NUCLEOPHILIC REAGENTS

No.	Compd	Attack at position	Method used[a]	Product
1	2,6-Dimethylthiopurine		E	
2	1-Methyl-2,6-dimethylthiopurine	6	A, B	15
3	3-Methyl-2,6-dimethylthiopurine	2	C	18
4	7-Methyl-2,6-dimethylthiopurine	6	D	23
5	9-Methyl-2,6-dimethylthiopurine	6	D	21
6	2,8-Dimethylthiopurine		E	
7	1-Methyl-2,8-dimethylthiopurine	2	D	17
8	6,8-Dimethylthiopurine		E	
9	3-Methyl-6-methylthio-8-chloropurine	6	$(SH^-)^b$	20
10	3-Methyl-6,8-dichloropurine	6	$(SH^-)^b$	20
11	2,6,8-Trimethylthiopurine		E	
12	1-Methyl-2,6,8-trimethylthiopurine	6	*c*	16
13	3-Methyl-2,6,8-trimethylthiopurine	2	C	19
14	9-Methyl-2,6,8-trimethylthiopurine	8	E	22

[a] For specification of the conditions used see Experimental Section. [b] With these purines, thiohydrolysis was tested instead of hydrolysis by OH^-. [c] 12 was so sensitive to hydrolysis that it could not be isolated in pure form.

1-Methyl-2,6-dimethylthiopurine (2) is hydrolyzed instantaneously by dilute ammonia at room temperature, or even by boiling water, at position 6 to yield the hypoxanthine 15 (Scheme I). The corresponding 1-methyl-2,6,8-trimethylthio derivative 12 is so sensitive to hydrolysis that it could not be isolated in pure form. Treatment of 1-methyl-2,8-dimethylthio-6-thiopurine (31, Scheme VI) with methyl iodide in DMF or acetonitrile, either at room temperature or at 70°, was ineffective. When the purine 31 was dissolved in dilute aqueous alkali and treated at room temperature with methyl iodide, the hypoxanthine 16 was obtained directly (Scheme VI). This result clearly demonstrates that in 12, again, the 6-SMe group is the most reactive one (Scheme I).

If, however, the 6-methylthio substituent is missing, as in 7, then alkali attacks at position 2 to give 17 (Scheme I). Combination of the results, obtained with 2, 12, and 7, permits us to establish for 1-methyl-2,6,8-trimethylthiopurine (12) the following sequence of reactivity toward nucleophilic reagents: $6 > 2 > 8$.

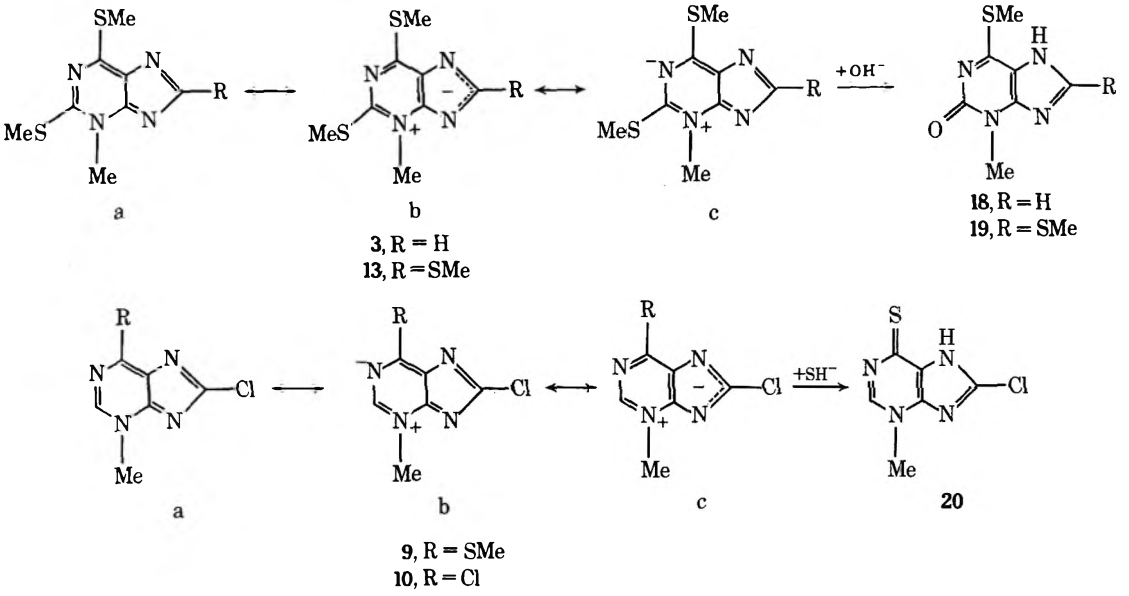
3-Methyl-2,6-dimethylthiopurine (3) and the corresponding trimethylthio derivative 13 both undergo hydrolysis at position 2 to yield 18 and 19, respectively (Scheme II). In order to determine whether position 6 or 8 follows next on the reactivity scale, we should test 3-methyl-6,8-dimethylthiopurine. However, this compound decomposed rapidly in alkaline media, and no defined product could be isolated. Therefore results are based on observations with 3-methyl-6-methylthio-8-chloropurine (9), which was found previously to react with sulfhydryl ion at position 6 to give 20,[10] although, as stated before, chloride ion is a much better leaving group than the methylmercaptide ion. In analogy, 3-methyl-6,8-dichloropurine (10) reacted with sulfhydryl ion first at position 6 to yield again 20[10] (see Scheme II). On this basis, we may derive for 3-methyl-2,6,8-trimethylthiopurine (13) the sequence $2 > 6 > 8$ for nucleophilic attack.

In 9-methyl-2,6,8-trimethylthiopurine (14), hydrolysis involves position 8 (22), while, in 9-methyl-2,6-dimethylthiopurine (5), position 6 is attacked first (21) (Scheme III). These results lead to the same order of reactivity as that established by Sutcliffe and Robins[5] for 9-methyl-TCP, *viz.*, $8 > 6 > 2$.

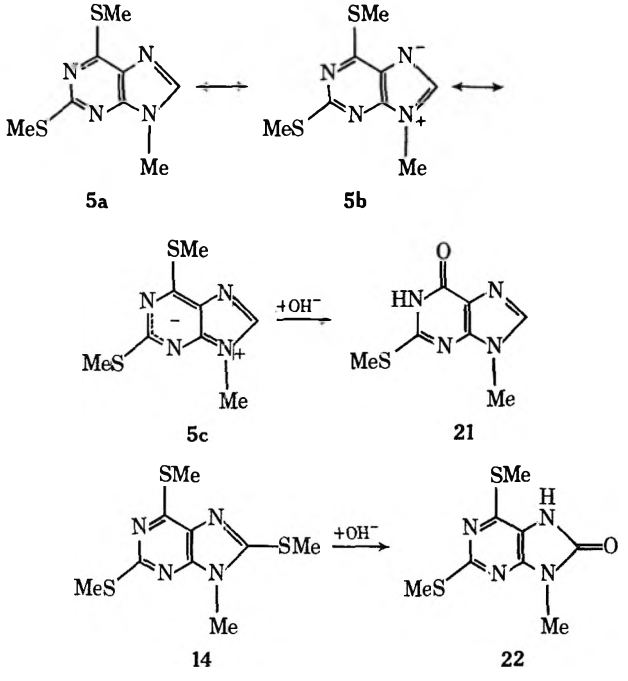
The 7-methyl derivative of 11 was not available. From the experiments with 7-methyl-TCP[5] and from our own observations with 7-methyl-2,6-dimethylthiopurine (4), which yielded the hypoxanthine 23 (Scheme IV), we suggest again the sequence $8 > 6 > 2$.

(7) S. F. Mason in "The Chemistry and Biology of Purines," Ciba Foundation Symposia, 1957, p 72.
(8) R. K. Robins, *J. Amer. Chem. Soc.*, **80**, 6671 (1958).
(9) A. G. Beaman and R. K. Robins, *J. Appl. Chem.*, **12**, 432 (1962).
(10) D. Diller, Z. Neiman, and F. Bergmann, *J. Chem. Soc. C*, 878 (1968).

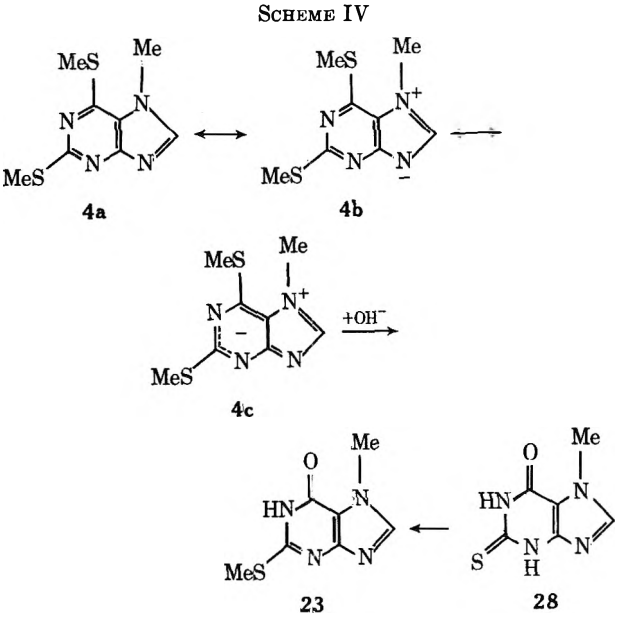
SCHEME II



SCHEME III



SCHEME IV



In Table I, we show also the various procedures used to split off the most reactive methylthio group in each case. Column 3 shows that the relative velocity for the various *N*-methyl derivatives is 1-Me ≫ 3-Me > 7-Me ~ 9-Me.

MO Calculations of Relative Susceptibility to Nucleophilic Attack.—Using Pullman's parametrization,[11] we have performed π-electronic Hückel-type calculations on methylthiopurines; the coefficients of the wave functions were subjected to a "frontier" analysis, as formulated by Fukui,[12] in order to obtain the superdelocalizabilities for nucleophilic attack. In these calculations, we have followed the same principle used above to determine the experimental sequences of reactivities. First, the site most susceptible to nucleophilic attack was derived for the isomeric *N*-methyl-2,6,8-trimethylthiopurines. Next, the susceptibility of the dimethylthiopurine, lacking the most reactive SMe substituent, was analyzed. The results in Table II (A) are in perfect agreement with the sequences found experimentally.

In a few cases (7- and 9-methyl-TCP,[5] 7-methyl-2,6-dichloropurine,[13] and **10**), the sequence of *N*-methylchloropurines for nucleophilic attack has been found identical with that established for the corresponding methylthio derivatives **4**, **5**, and **9**. Therefore we have also calculated the superdelocalizabilities for nucleophilic attack of *N*-methyldi- and -trichloropurines, following the principles explained above. Table II (B) not only shows agreement with the limited experimental data, but also predicts that, in this series, all sequences should be identical with those of the corresponding methylthiopurines.

(11) A. Pullman and B. Pullman, "Quantum Biochemistry," Interscience, New York, N. Y., 1963, p 108.

(12) K. Fukui, T. Yonezawa, and H. Shingu, *J. Chem. Phys.*, **20**, 722 (1952).

(13) R. N. Prasad and R. K. Robins, *J. Amer. Chem. Soc.*, **79**, 6401 (1957).

TABLE II

SEQUENCE OF NUCLEOPHILIC ATTACK, DERIVED FROM FUKUI'S SUPERDELOCALIZABILITIES[a]

Registry no.	Compd	Superdelocalizability for nucleophilic attack C-2	C-6	C-8	Sequence
	A. Methylthiopurines				
	1-Methyl-2,6,8-trimethylthiopurine (12)	0.898	*0.984*	0.846	6 > 2 > 8
	1-Methyl-2,8-dimethylthiopurine (7)	*0.896*		0.761	
	3-Methyl-2,6,8-trimethylthiopurine (13)	*0.825*	0.697	0.815	2 > 6 > 8
	3-Methyl-6,8-dimethylthiopurine		*0.877*	0.657	
	7-Methyl-2,6,8-trimethylthiopurine	0.720	0.724	*0.852*	8 > 6 > 2
	7-Methyl-2,6-dimethylthiopurine (4)	0.759	*0.795*		
	9-Methyl-2,6,8-trimethylthiopurine (14)	0.800	0.826	*0.889*	8 > 6 > 2
	9-Methyl-2,6-dimethylthiopurine (5)	0.773	*0.813*		
	B. Chloropurines				
39008-33-8	1-Methyl-2,6,8-trichloropurine	1.310	*1.865*	0.942	6 > 2 > 8
39008-34-9	1-Methyl-2,8-dichloropurine	*1.319*		0.963	
39008-35-0	3-Methyl-2,6,8-trichloropurine	*1.790*	1.763	0.974	2 > 6 > 8
18019-41-5	3-Methyl-6,8-dichloropurine		*1.793*	0.991	
16404-16-3	7-Methyl-2,6,8-trichloropurine	0.962	1.062	*1.283*	8 > 6 > 2
2273-93-0	7-Methyl-2,6-dichloropurine	0.963	*1.069*		
39008-39-4	9-Methyl-2,6,8-trichloropurine	0.997	1.104	*1.181*	8 > 6 > 2
2382-10-7	9-Methyl-2,6-dichloropurine	1.003	*1.113*		

[a] The most susceptible site in each derivative is italicized.

Discussion

In Fukui's method, the site most susceptible to nucleophilic attack is calculated. Resonance theory derives all possible polar forms of a heterocyclic molecule in its ground state, in most cases without any indication of their relative contributions. Moreover, the activation process during a chemical reaction may change these contributions in favor of one specific form. Nevertheless, we shall try in the following to discuss the probable course of the nucleophilic reactions of methylthiopurines in terms of resonance theory.

In the neutral molecules of **3**, **7**, **13**, and **14**, the methylthio group nearest to the *N*-methyl substituent is the first to suffer hydrolysis. Thus, in these cases, the attack of OH^- is clearly directed by the *N*-methyl group, presumably by virtue of its positive charge in the polarized molecule, as for instance in **3b** and **13b** (Scheme II). This type of electrostatic attraction is strongly enhanced during approach of the nucleophilic reagent; *i.e.*, **3b** and **13b** become predominant over **3c** and **13c**.

In the polarized forms of **2** and **12**, the negative charge is spread over position 3 (**2b** and **12b**) and the imidazole ring (**2c** and **12c**) (Scheme I). Thus, although the positive center at N-1 is at equal distance from the 2- and 6-methylthio substituents, the approach of OH^- to position 2 is less favored because of the adverse effect of the partial negative charge at N-3. Although mesomer c, in which the aromatic structure of the pyrimidine ring is preserved, probably makes a more important contribution, only mesomer b introduces a difference in the nucleophilicity of positions 2 and 6; thus attack at position 6 becomes predominant.

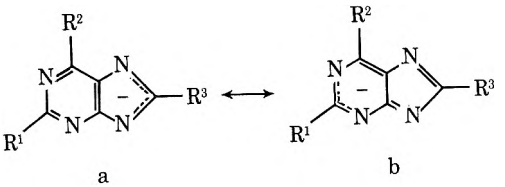
Similar considerations may be applied to those dimethylthiopurines in which hydrolysis of one SMe substituent is preferred, although the *N*-methyl group is not adjacent to any methylthio group. Thus, in the polarized forms of **9** and **10**, the negative charge is spread over N-1 (**9b**, **10b**) and the imidazole ring (**9c**, **10c**) (Scheme II). Here, mesomer c contributes more than the b form because of the aromatic structure of the pyrimidine ring in c and because of the participation of both N-7 and N-9 in the distribution of the negative charge. Mesomer c becomes even more predominant during the approach of the anion SH^-, so that thiohydrolysis of the 6 substituent in the pyrimidine moiety is preferred.

Similarly in the polarized forms of **4**, the negative charge is distributed between N-9 (**4b**), N-1, and N-3 (**4c**) (Scheme IV). Here attack at C-6 is preferred over C-2 for the following reasons: (a) the vicinity of the positive charge at N-7, (b) concentration of the negative charge in **4c** near position 2. Again we assume that the unequal distribution of negative charge is enhanced by the approach of the nucleophilic reagent.

The polarized forms of the 9-methyl derivative **5** indicate again a higher negative charge around C-2 than C-6 (Scheme III).

Similar reasoning can explain the sequence of hydrolysis in the anions of di- and trichloropurines. In the anion of TCP (**27**), the negative charge is distributed over the imidazole ring (**27a**), N-1, and N-3 (**27b**) (Scheme V). It is evident that only in **27a** is the aromatic structure of the molecule preserved and that the density of negative charge around C-6 is lower than in the vicinity of C-2. This explains the order of reactivity established for TCP[4,5] and similarly for 2,6-dichloropurine (**24**)[3] and its 6,8- (**25**)[8,9] and 2,8-dichloro isomers (**26**).[9] It should, however, be recalled that the absence of an *N*-methyl substituent and the concomitant lack of a positive center in these molecules

SCHEME V



24, $R^1 = R^2 = Cl$; $R^3 = H$
25, $R^1 = H$; $R^2 = R^3 = Cl_2$
26, $R^1 = R^3 = Cl$; $R^2 = H$
27, $R^1 = R^2 = R^3 = Cl$

makes attack of OH^- much more difficult. Thus Fisher[14] isolated crystalline salts of TCP with various metal cations; 6,8- and 2,8-dichloropurine required boiling 4 *N* NaOH to effect hydrolysis.[9]

In summary, the order of reactivity in methylthiopurines, and by analogy in chloropurines, can be explained qualitatively by the combined influence of three factors: (a) the polarity of the molecule, imposed by the presence of an *N*-methyl substituent; (b) the polarizability of the molecule, which enhances small differences in charge distribution during the approach of a nucleophilic reagent; and (c) the preference for resonance forms which preserve the aromatic character of the ring system.

Evidence for the Structure of the Oxopurines, Resulting from Hydrolysis of Methylthio Groups.—Compounds **15**[15] and **18**[16] were identical with known synthetic products. 7-Methyl-2-methylthiohypoxanthine (**23**) was synthesised independently by S-alkylation of the known 7-methyl-2-thioxanthine (**28**)[13] (see Scheme IV). Similarly, 3-methyl-6,8-dimethylthio-2-oxopurine (**19**) was prepared by methylation of 3-methyl-6,8-dithiouric acid (**29**) (see Experimental Section).

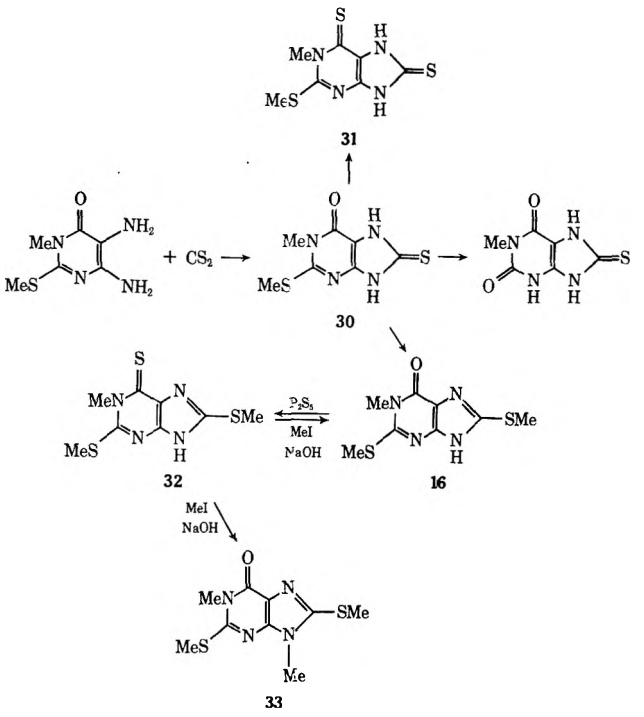
Identification of 1-methyl-8-methylthio-2-oxopurine (**17**) is based on the fact that the δ value of the 1-methyl group is shifted upfield by about 0.5 ppm upon hydrolysis of **7** (Table III). On the other hand, the 1-methyl signal is displaced only slightly by introduction of an oxo group into position 8. This is seen clearly in Table III by comparison of 1-methylpurine with 1-methyl-8-oxopurine and of other series of 1-methylpurines.

TABLE III
INFLUENCE OF OXO GROUPS ON THE CHEMICAL SHIFT OF THE 1-METHYL GROUP IN PURINES

Registry no.	Compd	δ_{NMe}, ppm, of neutral molecule
21802-40-4	1-Methylpurine	4.20
1008-40-8	1-Methyl-6-methylthiopurine	4.12
1125-39-9	1-Methylhypoxanthine	3.65
39008-42-9	1-Methyl-8-oxopurine	4.19
	1-Methyl-2,6-dimethylthiopurine (**2**)	4.10
38759-23-8	1-Methyl-6-methylthio-2-oxopurine	3.69
39008-44-1	1-Methyl-8-methylthio-2-oxopurine	3.61
39008-45-2	1-Methyl-6-methylthio-8-oxopurine	4.21
	1-Methyl-2-methylthiohypoxanthine (**15**)	3.46
	1-Methyl-2,8-dimethylthiopurine (**7**)	4.06
	1-Methyl-2,8-dimethylthiohypoxanthine (**16**)	3.65
	1-Methyl-8-methylthio-2-oxopurine (**17**)	3.60

1-Methyl-2,8-dimethylthiohypoxanthine (**16**) was synthesized from 1-methyl-2-methylthio-6-oxo-8-thiopurine (**30**), as shown in Scheme VI.

SCHEME VI



The structure of 9-methyl-2-methylthiohypoxanthine (**21**) is derived from the fact that this compound differs from the alternative product of hydrolysis of **5**, *viz.*, 9-methyl-6-methylthio-2-oxopurine, which has been described recently.[17]

Finally, the structure of 9-methyl-2,6-dimethylthio-8-oxopurine (**22**) was established by elementary analysis, by uv and nmr spectra, and by the fact that this compound differed from the other two possible products of hydrolysis of **14**, *viz.*, 9-methyl-2,8-dimethylthiohypoxanthine (**34**) and 9-methyl-6,8-dimethylthio-2-oxopurine (**36**), which both were obtained by unequivocal procedures (see Table IV and V and Experimental Section).

Experimental Section

All melting points were determined on a Fisher-Johns apparatus and are uncorrected. Analyses were by M. Goldstein, Jerusalem. Uv spectra were measured on a Hitachi Perkin-Elmer Model 124 spectrophotometer and nmr spectra on a Jeol MH-100 instrument, using TSP (sodium 3-trimethylsilylpropionate-*2,2,3,3-d*$_4$ of Merck, Sharp and Dohme, Canada) as internal standard.

For descending chromatography on Whatman paper No. 1, the following solvents were used: A, 1-butanol–acetic acid–water (12:3:5, v/v); B, ethanol–DMF–water (3:1:1, v/v). Spots were located by their fluorescence under a Mineralight UV lamp ($\lambda \sim 254$ nm).

General Procedures. S-Methylation of thiopurines was carried out at room temperature by stirring a solution of the substrate in 1 *N* NaOH with 2 equiv of methyl iodide. The product was precipitated by neutralization with glacial acetic acid.

Hydrolysis of Methylthiopurines. Method A.—A suspension of the substrate in water was refluxed until all the material had gone into solution. The product crystallized upon cooling.

Method B.—A solution of the methylthio derivative in 25% ammonia was kept at room temperature for 10 min.

Method C.—A suspension of the substrate in $NaHCO_3$ was stirred and refluxed for 2 hr. The solution was brought to pH 6 by addition of glacial acetic acid and the precipitate was purified.

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TABLE IV
NEW OXO- AND THIOPURINES

Compd	No.	Mp, °C	Procedure	λ_{max}, nm (log ϵ_{max}), at pH 1	λ_{max}, nm (log ϵ_{max}), at pH 6	λ_{max}, nm (log ϵ_{max}), at pH 12	Solvent for crystn	Crystal form and color	R_f A	R_f B	Fluorescence
A. 1-Methyl Derivatives											
1-Methyl-8-methylthio-2-oxopurine	**17**	>300	From **7**	346 (4.45)	330 (4.04)	286 (4.06) 330 (4.06)	Ethanol	Colorless prisms	0.61	0.51	Bright violet
1-Methyl-2-methylthio-6-oxo-8-thiopurine	**30**	>300	See Scheme VI		253[a] 296				0.7	0.75	Dark violet
1-Methyl-6,8-dithio-2-methylthiopurine	**31**	>300	From **30**		279[a] 369		NaOH–acetic acid	Yellow microcrystals	0.62	0.68	Dark violet
1-Methyl-2,8-dimethylthiohypoxanthine	**16**	275	From **12** and **30**	225 (4.40) 283 (4.47)	280 (4.39)	235 (4.40) 286 (4.36)	Ethanol	Colorless prisms	0.85	0.75	Dark violet
1-Methyl-2,8-dimethylthio-6-thiopurine	**32**	295	From **31**		263[b] 350		Benzene	Yellow needles	0.78	0.73	Dark violet
B. 3-Methyl Derivatives											
3-Methyl-6,8-dithiouric acid	**29**	>300	See Experimental		289[c] 392		NaOH–acetic acid	Yellow microcrystals	0.43	0.71	Brown
3-Methyl-6,8-dimethylthio-2-oxopurine	**19**	268–270	From **29** and **13**	279 (4.04) 370 (4.59)	342 (4.47)	340 (4.45)	Ethanol	Colorless needles	0.84	0.75	Bright violet
C. 7-Methyl Derivatives											
7-Methyl-2-methylthiohypoxanthine	**23**	>300	From **27**	266 (4.27)	225 (4.12) 265 (4.22)	233 (4.45) 274.5 (4.15)	H_2O	Colorless prisms	0.74	0.73	Dark violet
D. 9-Methyl Derivatives											
9-Methyl-6,8-dithiouric acid	**35**	>300	See Experimental	269 307 377	264 309 371		Ammonia–acetic acid	Yellow microcrystals	0.23	0.68	Brown
9-Methyl-2-methylthiohypoxanthine	**21**	>300	From **5**	266 (4.32)	263 (4.20)	272.5 (4.20)	H_2O	Colorless prisms	0.76	0.75	Dark violet
9-Methyl-2,6-dimethylthio-8-oxopurine	**22**	274–275	From **14**	255 (4.25) 316 (4.06)	256 (4.19) 315 (4.09)	286 (4.04) 324 (4.02)	Ethanol	Colorless needles	0.85	0.77	Bright violet
9-Methyl-2,8-dimethylthiohypoxanthine	**34**	>300	See Experimental	283 (4.20)	280 (4.21)	286 (4.24)	1-Butanol	Colorless plates			
9-Methyl-6,8-dimethylthio-2-oxopurine	**36**	276–277	From **35**	248 (4.41) 357 (4.30)	330 (4.28)	327 (4.34)	Ethanol	Colorless rods	0.78	0.71	Greenish blue

[a] Measured only at pH 8.0. [b] Because of the lack of material, the spectrum was measured only in methanol. [c] Measured only at pH 7.0.

TABLE V

No.	Formula	Molecular weight	Analysis, % Calcd C	H	N	S	Found C	H	N	S
17	$C_7H_8N_4OS$	196	42.9	4.1	28.6	16.3	42.7	4.0	28.5	16.2
21	$C_7H_8N_4OS$	196	42.9	4.1	28.6	16.3	42.5	3.9	28.2	16.0
23	$C_7H_8N_4OS$	196	42.9	4.1	28.6	16.3	42.9	4.0	28.3	16.1
29	$C_6H_6N_4OS_2$	214	33.6	2.8	26.2	29.9	33.3	2.6	25.9	29.4
35	$C_6H_6N_4OS_2$	214	33.6	2.8	26.2	29.9	33.2	2.7	25.9	29.5
16	$C_8H_{16}N_4OS_2$	242	39.7	4.1	23.1	26.4	39.6	4.1	23.0	26.3
19	$C_8H_{10}N_4OS_2$	242	39.7	4.1	23.1	26.4	39.5	4.1	23.0	26.2
22	$C_8H_{10}N_4OS_2$	242	39.7	4.1	23.1	26.4	39.4	4.0	23.1	26.3
34	$C_8H_{10}N_4OS_2$	242	39.7	4.1	23.1	26.4	39.4	4.2	22.9	26.1
36	$C_8H_{10}N_4OS_2$	242	39.7	4.1	23.1	26.4	39.2	3.9	22.7	26.0
31	$C_7H_8N_4S_3$	244	34.4	3.3	23.0	39.3	34.2	3.1	22.6	38.8
32	$C_8H_{10}N_4S_3$	258[a]	37.2	3.9	21.7	37.2	37.7	4.1	22.1	36.8

[a] Measured by mass spectrum; nmr ($CDCl_3$) δ 2.76 (s, 2-SMe), 2.84 (s, 8-SMe), 4.16 (s, 1-NMe) ppm.

Method D.—A suspension of the methylthiopurine in 2 *N* NaOH was refluxed for 20 min. The clear solution was brought to pH 6 by addition of glacial acetic acid.

Method E.—A suspension of the substrate in a mixture of 2 *N* NaOH–methanol (4:1) was stirred and refluxed for 30 min. The methanol was removed *in vacuo* and the clear aqueous solution was acidified with glacial acetic acid.

Purines.—The following compounds were prepared according to known procedures: 2,6-dimethylthiopurine (**1**)[18] and its 7-methyl derivative **4**;[13] the other *N*-methyl derivatives of **1**, *viz.*, **2**, **3**, and **5**;[19] 2,8-dimethylthiopurine (**6**)[20,21] and its 1-methyl derivative **7**;[19] 6,8-dimethylthiopurine (**8**),[8] its 3-methyl derivative,[19] and **9** and **10**;[10] 2,6,8-trimethylthiopurine (**11**)[21] and its methyl derivatives **13** and **14**;[19] 1-methyl-2-methylthiohypoxanthine (**15**)[15] and 3-methyl-6-methylthio-2-oxopurine (**18**).[16]

New Compounds. 1-Methyl-2,8-dimethylthiohypoxanthine (16) and Derivatives. A. 1-Methyl-2-methylthio-6-oxo-8-thiopurine (30; See Scheme VI).—A solution of 4,5-diamino-1-methyl-2-methylthio-6-oxopyrimidine[15] (3 g) in pyridine (120 ml) and carbon disulfide (10 ml) was refluxed for 5 hr. The residue, remaining after evaporation of the volatile components, was stirred and heated with water (100 ml) for 10 min. The insoluble brown portion was filtered off and dissolved in 1 *N* NaOH, and the reaction product was precipitated by glacial acetic acid, mp >300° dec (3 g, 82%) (for physical properties see Table IV). Although this compound was not easily purified, its structure was established by hydrolysis with 6 *N* HCl to 1-methyl-8-thiouric acid[22] (see Scheme VI).

B. 1-Methyl-2,8-dimethylthiohypoxanthine (16).—A solution of **30** (1 g) in DMF (50 ml) and methyl iodide (2 ml) was kept at room temperature for 12 hr. The solvent was removed *in vacuo* and the residue was treated with a small amount of cold water. The insoluble portion was dissolved in 1 *N* NaOH and the product was precipitated by neutralization with glacial acetic acid, mp 275°. The compound was identical in all respects with purine **16**, described below (see also Table IV).

C. 1-Methyl-2-methylthio-6,8-dithiopurine (31).—A solution of **30** (3 g) in β-picoline (150 ml) was stirred with phosphorus pentasulfide (6 g) and refluxed for 6 hr. The solvent was evaporated *in vacuo* and the residue was heated with water (250 ml) for 15 min. The insoluble portion was purified, as described under A, as yellow microcrystals (3 g, 93%), mp >300° dec. For physical properties and analysis see Table IV.

D. 1-Methyl-2,8-dimethylthio-6-thiopurine (32).—A solution of the dithio derivative **31** (2 g) in DMF (50 ml) and methyl iodide (5 ml) was kept at room temperature for 12 hr. The solvent was distilled off *in vacuo*, the residue was dissolved in 1 *N* NaOH, and the product was precipitated by addition of glacial acetic acid. From ethyl acetate were obtained yellow needles, mp 295° (1 g, 47%) (see Table IV).

The 6-thio group was not methylated even in boiling DMF. When either **31** or **32** were dissolved in sodium hydroxide and treated at room temperature with methyl iodide, a mixture of two products was obtained. The substance, separating directly from the reaction mixture, was identified as 1,9-dimethyl-2,8-dimethylthiohypoxanthine (**33**).[22] Acidification of the filtrate yielded **16**, identical with the product described under B.

3-Methyl-6,8-dimethylthio-2-oxopurine (19). A. 3-Methyl-6,8-dithiouric Acid (29).—A solution of 4,5-diamino-3-methyl-6-thiouracil (**23**) (21 g) in pyridine (170 ml) and carbon disulfide (21 ml) was stirred and refluxed for 5 hr in the presence of powdered sodium hydroxide (2 g). The solvent was removed *in vacuo* and the residue was dissolved in 2 *N* NaOH. After decolorization with charcoal, the filtrate was brought first to exactly pH 7 with hydrochloric acid and then to pH 6 by addition of acetic acid. The precipitate was purified by repetition of this method as yellow microcrystals (15 g, 57%), mp >300° dec (see Table IV).

B. 3-Methyl-6,8-dimethylthio-2-oxopurine (19).—A solution of the foregoing product (1 g) in 2 *N* NaOH was methylated according to the method described under General Procedures (see Table IV).

7-Methyl-2-methylthiohypoxanthine (23).—**23** was prepared by methylation of 7-methyl-2-thioxanthine (**28**),[13] using the general procedure described above, mp >300° (see Table IV).

9-Methyl-2,8-dimethylthiohypoxanthine (34).—A solution of 9-methyl-2,8-dithiouric acid[19] (1 g) in 2 *N* NaOH (150 ml) was stirred with methyl iodide (2 ml) at room temperature for 1 hr. The precipitate, formed upon neutralization, crystallized from 1-butanol as colorless plates, mp >300° (see Table IV).

9-Methyl-6,8-dimethylthio-2-oxopurine (36). A. Synthesis of 9-Methyl-6,8-dithiouric Acid (35).—A mixture of 9-methyl-8-thiouric acid[23] (5 g), phosphorus pentasulfide (10 g), and pyridine (300 ml) was stirred and refluxed for 4 hr. The solvent was removed *in vacuo* and the residue was treated with boiling water (250 ml) for 15 min. The insoluble portion was dissolved in 25% ammonia (charcoal) and the product was precipitated by neutralization with glacial acetic acid as yellow microcrystals (3 g, 56%), mp >300° dec (see Table IV).

B. 9-Methyl-6,8-dimethylthio-2-oxopurine (36).—Methylation of an alkaline solution of the foregoing product with methyl iodide was carried out as described before; colorless rods (ethanol) (90%) were obtained, mp 276–277° (see Table IV).

Calculation of Superdelocalizabilities.—The Hückel topological matrices were constructed, using the appropriate parametrization of the Coulomb and resonance integrals. After diagonalization (Jacobi's method), the wave functions and energies were subjected to a "frontier" calculation according to the formulation of Fukui.[12] All computations were performed on a CDC 6400 digital computing machine using a Fortran program.

Registry No.—**1**, 39008-18-9; **2**, 39008-19-0; **3**, 39008-20-3; **4**, 39008-21-4; **5**, 39008-22-5; **6**, 39008-23-6; **7**, 39008-24-7; **8**, 39008-23-6; **9**, 18019-39-1; **10**, 18019-41-5; **11**, 39013-71-3; **12**, 39013-72-4; **13**, 39013-73-5; **14**, 39013-74-6; **15**, 33867-98-0; **16**, 39013-76-8; **17**, 39008-44-1; **19**, 39013-78-0; **21**, 39013-79-1; **22**, 39057-19-7; **23**, 39013-80-4; **28**, 39013-81-5; **29**, 39013-82-6; **30**, 39013-83-7; **31**,

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39013-84-8; **32**, 39008-25-8; **34**, 39062-23-2; **35**, 39008-26-9; **36**, 39008-27-0; 4,5-diamino-1-methyl-2-methylthio-6-oxopyrimidine, 39008-28-1; carbon disulfide, 75-15-0; 9-methyl-2,8-dithiouric acid, 39008-29-2; 9-methyl-8-thiouric acid, 39008-30-5; 3-methyl-6,8-dimethylthiopurine, 39008-31-6; 7-methyl-2,6,8-trimethylthiopurine, 39008-32-7.

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Pteridines. I. β-Keto Sulfoxides and α-Keto Aldehyde Hemithioacetals as Pteridine Precursors. A New Selective Synthesis of 6- and 7-Substituted Pteridines[1]

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Alkyl and aralkyl β-keto sulfoxides are converted into 2-amino-4-hydroxypteridines on treatment with 2,4,5-triamino-6-hydroxypyrimidine sulfate and sodium acetate in glacial acetic acid at room temperature for 0.5–1.0 hr followed by refluxing for 1 hr. The only pteridines isolated under these specific conditions are the 6 isomers, with no 7 isomers detected by uv or nmr analysis. In order to account for the positional selectivity of the reaction, a mechanism is proposed wherein β-keto sulfoxides are viewed as "latent" α-keto aldehydes. A regiospecific synthesis of the isomeric 7-substituted pteridines is also described, involving the use of α-keto aldehyde hemithioacetals. Nmr spectra of the 6- and 7-substituted pteridines in FSO_3H and in 1:4 FSO_3H–CF_3CO_2H solution are reported.

The problem of devising a direct and unequivocal route to 6-substituted pteridines has long challenged the imagination of synthetic organic chemists.[2] In the classical approach, condensation of α-keto aldehydes with 4,5-diaminopyrimidines leads to varying mixtures of 6- and 7-substituted products, even in the presence of "aldehyde-protecting" reagents such as sodium bisulfite,[3,4] hydrazine,[5,6] or 2-mercaptoethanol.[7] Similarly, α-keto aldehyde derivatives with the aldehyde function blocked in the form of an acetal[8] or hydrazone[8] afford mixtures because acid-catalyzed partial dissociation to the free aldehyde cannot be completely prevented.[6] Although several alternatives have been developed in order to circumvent these difficulties, they all involve lengthy and sometimes inefficient reaction schemes. Familiar examples include several variants[9,10] of the homofolic and bishomofolic acid synthesis,[11] and also the ingenious pyrazine route devised recently by Taylor and coworkers.[12] This report describes a new pteridine synthesis which is notable for its simplicity and appears to proceed with remarkable positional selectivity. The key element in our approach was the novel use of β-keto sulfoxides,[13] a readily accessible class of compounds whose acid-catalyzed transformations[14,15] allow them to be viewed as "latent" α-keto aldehydes.[16,17]

A representative group of β-keto sulfoxides (**1a–f**), obtained from the appropriate esters *via* the dimethyl sulfoxide–sodium hydride procedure,[13,15] was allowed to react with 2,4,5-triamino-6-hydroxypyrimidine. In every instance the pteridine products were identified as 6-substituted derivatives (**2a–f**), with no evidence for the formation of 7 isomers.

In accord with considerations of a possible mechanism (see Chart I), the reaction was conducted in two stages. After equimolar amounts of each β-keto sulfoxide and of the pyrimidine (in the form of its sulfate salt) were suspended in glacial acetic acid containing 2 molar equiv of sodium acetate, the heterogeneous mixture was

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(2) For a review of recent advances, see "Chemistry and Biology of Pteridines, Proceedings of the Fourth International Symposium on Pteridines, Toba, July 1969," K. Iwai, Ed., International Academic Printing Co., Tokyo, Japan, 1970.

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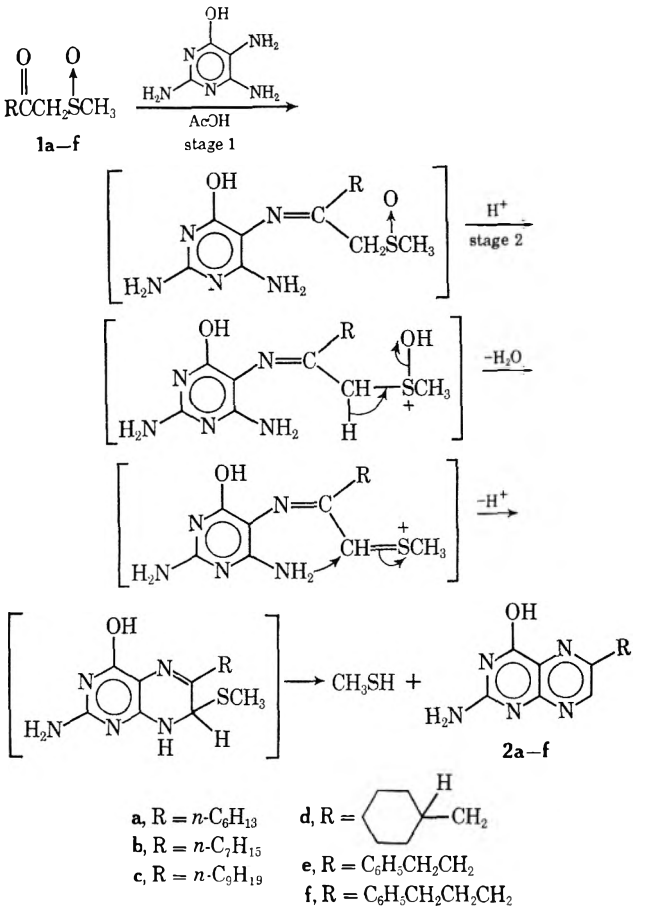
(16) In the context of this work use of the term "latent" is intended to denote the fact that in β-keto sulfoxides, as opposed to acetals, hydrazones, or other true aldehyde derivatives, the carbon destined to become an aldehyde is not yet in the aldehyde oxidation state at the start of the reaction.

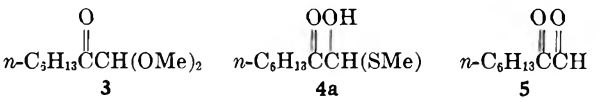
(17) Following the completion of this work an interesting example illustrating the use of a β-keto sulfoxide as a "latent" α-keto aldehyde appeared; see M. von Strandtman, D. Connor and J. Shavel, Jr., *J. Heterocycl. Chem.*, **9**, 175 (1972).

CHART I



stirred at room temperature for 0.5–1.0 hr in order to form the putative Schiff base intermediate (stage 1) shown in Chart I, and then under reflux for 1 hr to effect a Pummerer-like rearrangement and concomitant ring closure (stage 2). Pteridine formation was signaled by copious evolution of methyl mercaptan as soon as heating was begun. Purification of the resultant 6-substituted pteridines (**2a–f**) was achieved very effectively in most instances by a single crystallization from 80% formic acid.

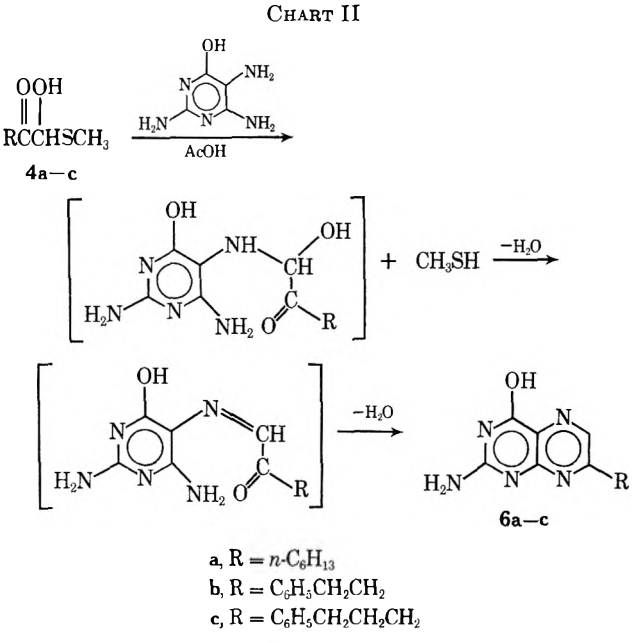
In order to assess the synthetic validity of the keto sulfoxide approach, we also carried out parallel experiments with other potential pteridine precursors, including the parent α-keto aldehyde itself. The *n*-hexyl series was selected for this purpose. Keto sulfoxide **1a** was converted into 1,1-dimethoxy-2-octanone (**3**, 91% yield) by reaction with methanol and iodine[15] and into 1-methylthio-1-octanol-2-one (**4a**, 79% yield) on treatment with HCl in DMSO.[14b] Heating **4a** under reduced pressure, in an attempted distillation, unexpectedly led to the formation of 1,2-octanedione (**5**, 39% yield). This provided a straightforward alternative to the reported copper acetate technique.[14b] The identity and purity of each compound was established rigorously by nmr. Dimethyl acetal **3** displayed sharp singlets at δ 4.43 for the methinyl proton and at δ 3.42 for the methoxy proton, whereas methyl hemithioacetal **4a** showed singlets at δ 5.30 and 3.62 for the methinyl and methylthio protons, respectively. Keto aldehyde **5**, on the other hand, exhibited a typical sharp singlet at δ 9.21 which was totally absent in **3** and **4a**. The latter were thus entirely free of keto aldehyde.



When dimethyl acetal **3** was allowed to react with 2,4,5-triamino-6-hydroxypyrimidine under the same conditions as had been used with **1a** the product was found on the basis of uv and nmr analysis (see Experimental Section) to contain both pteridine **2a** and its 7 isomer **6a**. In the reaction of **3** the proportion of **6a** was estimated to be only 10–15% (nonetheless a troublesome contamination in view of the known difficulty of separation of pteridine isomers), whereas with **5** the two products were formed in approximately equal amounts. When the same reaction was carried out with hemithioacetal **4a**, however, the sole product (74% yield) proved to be **6a**. We thus had at our disposal, complementing the keto sulfoxide technique, a second route capable of giving 7 isomers exclusively.

As a further illustration of the general utility of the hemithioacetal route to 7-substituted pteridines, keto sulfoxides **1e** and **1f** were converted into hemithioacetals **4b** and **4c** (70–80% yield) and these stable crystalline derivatives were in turn allowed to react with 2,4,5-triamino-6-hydroxypyrimidine in order to form **6b** and **6c**, respectively. A reasonable mechanism for this reaction is shown in Chart II. The unidirectional course

CHART II



of the reaction may be due mostly to the ease of breakage of the C–S bond, methyl mercaptan formation thereby taking precedence over Schiff base formation in the first step.

Because all the pteridines prepared in this work were high-melting compounds, melting point determinations were of little value in establishing identity or purity. Paper chromatography was likewise considered a dubious criterion in view of the very close R_f values reported by other workers for 6 and 7 isomers in various solvent systems.[8,18] Uv and nmr spectra, on the other hand, provided an effective tool for this purpose and were in qualitative accord with the literature. Thus,

(18) F. Weygand, H. Simon, K. D. Keil, and H. Millauer, *Chem. Ber.*, **97**, 1002 (1964).

uv spectra of the 6-substituted pteridines **2a–f** measured in 0.1 *N* NaOH solution all had E_{255}/E_{365} values (extinction coefficient ratios)[5b,6–8] of 3.4–3.6, whereas those of the 7 isomers **6a–c** all showed E_{255}/E_{365} values of 2.4–2.5. Moreover, nmr spectra determined in a 1:4 FSO_3H–CF_3CO_2H mixture or in certain instances in FSO_3H alone were consistent with the findings of Dieffenbacher and Philipsborn,[19a] who reported a chemical shift difference of 0.6 ppm between 2-amino-4-hydroxy-6-methylpteridine and 2-amino-4-hydroxy-7-methylpteridine. This increment, which is greater than can be observed with trifluoroacetic acid[19b] or in 0.1 *N* NaOD solution,[7] has been ascribed to the ability of FSO_3H to diprotonate the pteridine ring at N-1 and N-8. Because of the proximity of a positive charge in the dication, the C-7 proton in a 6-substituted pteridine gives rise to a resonance signal at a lower magnetic field than the 6 proton in the corresponding 7 isomer. In the present series the 6-alkylpteridines **2a–d** gave spectra with sharp singlets at δ 9.7 in 1:4 FSO_3H–CF_3CO_2H and at 9.9 in FSO_3H alone. In contrast, the spectrum of 7-alkylpteridine **6a** in 1:4 FSO_3H–CF_3CO_2H solution displayed a sharp singlet at δ 9.0.[20]

Although nmr spectra could also be used to distinguish 6- and 7-aralkyl derivatives, the presence of phenyl groups susceptible to electrophilic attack was a complicating factor.[21] Thus, a sample of **2f** freshly dissolved in 1:4 FSO_3H–CF_3CO_2H showed the C-7 proton and phenyl protons as singlets at δ 8.6 and 7.3, respectively. However, an almost immediate change began to occur in the spectrum. The C-7 proton signal at δ 8.6 decreased rapidly and was replaced by another singlet at δ 9.6. At the same time the phenyl singlet gave way to an AB quartet at δ 7.8 consistent with para substitution on the aromatic ring. The spectral transformation was complete after 2 hr at magnet temperature (*ca.* 40°). A fresh solution of **6c** in 1:4 FSO_3H–CF_3CO_2H also showed singlets at δ 8.7 (C-6 proton) and 7.3 (phenyl protons) which decreased rapidly in intensity with the emergence of a new singlet at δ 9.0 and an AB quartet at δ 7.8 (the change was complete in this instance after only 45 min). It is possible that the δ 8.7 singlet in the spectra of **2e** and **6c** represents a transient monoprotonated species, since a spectrum of **2e** in CF_3CO_2H alone likewise contained a singlet at δ 8.7.

In addition to the foregoing uv and nmr spectral data, more direct chemical evidence was obtained with several compounds. Oxidation of pteridines **2a**, **2c**, and **2d** with alkaline potassium permanganate afforded 2-amino-4-hydroxypteridine-6-carboxylic acid, identified by comparison (ir, uv, and paper chromatography) with an authentic specimen derived from 2-amino-4-hydroxy-6-methylpteridine.[6] Similar oxidation of **6a** furnished 2-amino-4-hydroxypteridine-7-carboxylic acid, shown to be identical with an authentic specimen prepared by oxidation of 2-amino-4-hydroxy-7-methylpteridine.[6] Control experiments with mixtures of **2a** and its 7 isomer **6a** yielded mixtures of the 6- and 7-carboxylic acids whose ir and uv spectral characteristics were readily distinguishable from those of either pure acid alone.

The yields of pteridines obtained *via* the β-keto sulfoxide route (9–17%) and the α-keto aldehyde hemithioacetal route (45–75%) merit some discussion. For reasons of convenience, all the reactions were carried out under uniform conditions, which may not necessarily have been optimal for each compound. With both types of precursors there was considerable formation of nonpteridine by-products which remained in solution during recrystallization from 80% formic acid. In addition, however, there was some decomposition of the β-keto sulfoxides, as judged from the malodorous character of the mother liquors. We conclude that the higher yield of 7 isomers is a consequence of the fact that the hemithioacetals are less prone than the β-keto sulfoxides to undergo side reactions. It might be possible to lessen the impact of these side reactions by altering various parameters such as the duration of stage 1 or the pH. However, it is important to stress that, even with yields not exceeding 20%, the β-keto sulfoxide route nonetheless compares quite favorably with older methods wherein removal of small quantities of 7 isomer by repetitive fractional crystallization is extremely laborious and is known to result frequently in large material losses. A fuller assessment of the synthetic potential of β-keto sulfoxides and α-keto aldehyde hemithioacetals as pteridine precursors awaits investigation.

Experimental Section[22]

1-Methylsulfinyl-2-octanone (1a) (Procedure A).—NaH (21 g of 57% mineral oil dispersion, 0.5 mol) was placed in a 500-ml three-necked flask equipped with a mechanical stirrer, pressure-equalized dropping funnel, reflux condenser, and T tube leading to a nitrogen cylinder and water aspirator. After repeated treatment with *n*-hexane to remove the mineral oil, DMSO (250 ml, dried over Linde 3A Molecular Sieves) was added and the stirred mixture was heated to *ca.* 75° by means of an oil bath, a positive nitrogen atmosphere being maintained. When hydrogen evolution was complete (2–3 hr) the dark gray solution was cooled to room temperature, ethyl *n*-heptanoate (40 g, 0.25 mol) was added dropwise, and the mixture was stirred for 1 hr and poured into ice–water (450 ml). After Et_2O extraction to remove unreacted ester the aqueous phase was cooled and acidified to pH 2 with 12 *N* HCl (50 ml). Extraction with $CHCl_3$ (700 ml), washing with H_2O and saturated NaCl, drying, and evaporation under reduced pressure left a solid which crystallized from *i*-Pr_2O in the form of colorless prisms (38 g, 81%), mp 63–64°.

Anal. Calcd for $C_9H_{18}O_2S$: C, 56.80; H, 9.53; S, 16.85. Found: C, 57.02; H, 9.73; S, 17.05.

1-Methylsulfinyl-2-nonanone (1b).—This compound was prepared in 76% yield *via* procedure A, starting from ethyl *n*-octanoate, as colorless prisms, mp 63–64° (*i*-Pr_2O–*n*-hexane).

(19) (a) A. Dieffenbacher and W. von Philipsborn, *Helv. Chim. Acta*, **52**, 743 (1969); (b) A. Dieffenbacher, R. Mondelli, and W. von Philipsborn,, *ibid.*, **49**, 1355 (1966).

(20) The nmr spectrum of **6a** in FSO_3H alone underwent progressive changes, the initial C-7 methylene triplet at δ 3.6 giving way to a new triplet at δ 5.5 suggestive of a vinyl proton. The transformation was essentially complete after 3 hr. It appears therefore that, whereas 6-alkyl compounds are stable in FSO_3H solution, the 7 isomers are not.

(21) It is reasonable to suppose that 1:4 FSO_3H–CF_3CO_2H mixtures contain significant amounts of the known mixed anhydride $CF_3C(O)OSO_2F$ [D. D. DesMarteau and G. H. Cady, *Inorg. Chem.*, **5**, 169 (1966)], which could serve as a powerful electrophilic reagent [*cf.* F. Carré, R. Corriu, and G. Dabosi, *Bull. Soc. Chim. Fr.*, 2905 (1967), and M. H. Karger and Y. Mazur, *J. Org. Chem.*, **36**, 540 (1971)].

(22) Ir spectra were taken with a Perkin-Elmer Model 137B double-beam recording spectrophotometer. Quantitative uv spectra were measured on Cary Model 11 and 15 spectrophotometers. Nmr spectra were determined on a Varian A-60 instrument with Me_4Si as the reference. When FSO_3H was used as the solvent a sealed capillary containing Me_4Si was placed in the nmr sample tube. For paper chromatography by the ascending or descending technique the following solvent systems were used: (1) *n*-BuOH–morpholine–H_2O (3:1:2); (2) *i*-PrOH–1 *N* NH_4OH (7:3); (3) 5% Na_2CO_3; (4) *i*-PrOH–concentrated NH_4OH–H_2O (7:2:1); (5) *n*-BuOH–AcOH–H_2O (4:1:5); (6) *i*-PrOH–concentrated NH_4OH–H_2O (5:1:2). Melting points were measured in Pyrex capillary tubes in a Mel-Temp apparatus (Laboratory Devices, Inc., Cambridge, Mass.) and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by Werby Laboratories, Boston, Mass.

Anal. Calcd for $C_{10}H_{20}O_2S$: C, 58.72; H, 9.86; S, 15.66. Found: C, 58.57; H, 10.00: S, 15.60.

1-Methylsulfinyl-4-phenyl-2-butanone (1e).—This compound was prepared from methyl hydrocinnamate *via* procedure A: 55% yield; mp 54–56° (*i*-Pr_2O–$CHCl_3$); nmr ($CDCl_3$) δ 3.70 (d, J = 1.0 Hz, 2, $COCH_2SO$), 2.93 (s, 4, CH_2CH_2), 2.58 (s, 3, CH_3SO).

Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.84; H, 6.71; S, 15.22. Found: C, 62.58; H, 6.77; S, 15.50.

1-Methylsulfinyl-5-phenyl-2-pentanone (1f).—This compound was prepared from methyl 4-phenylbutyrate *via* procedure A: 85% yield; mp 44–47° (*i*-Pr_2O–$CHCl_3$); nmr ($CDCl_3$) δ 3.70 (s, 2, $COCH_2SO$), 2.4–2.9 (m, 4) and 1.7–2.2 (m, 2) ($CH_2CH_2CH_2$), 2.63 (s, 3, CH_3SO).

Anal. Calcd for $C_{12}H_{16}O_2S$: C, 64.27; H, 7.19; S, 14.26. Found: C, 64.42; H, 7.38; S, 14.49.

1-Methylthio-4-phenyl-1-butanol-2-one (4b) (Procedure B).—A mixture of **1e** (5 g, 0.024 mol), DMSO (9.1 ml), H_2O (68 ml), and 12 *N* HCl (9.1 ml) was stirred at room temperature for 24 hr. Extraction with Et_2O (100 ml), washing with 5% $NaHCO_3$ and H_2O, drying, evaporation under reduced pressure, and recrystallization of the residue (3.5 g, 70%) from $CHCl_3$–petroleum ether (bp 30–60°) gave colorless prisms: mp 49–50°; nmr ($CDCl_3$) δ 5.18 (d, 1, methine H), 4.08 (s, 1, OH), 2.97 (m, 4, CH_2CH_2), 1.82 (s, 3, CH_3S), in accord with assignments reported for arylglyoxal hemithioacetals.[14b]

Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.84; H, 6.71; S, 15.22. Found: C, 62.98; H, 6.76; S, 15.17.

1-Methylthio-5-phenyl-1-pentanol-2-one (4c).—This compound was prepared from β-keto sulfoxide **1f** *via* procedure B: 76% yield; mp 83–84.5° ($CHCl_3$–petroleum ether); nmr ($CDCl_3$) δ 5.2 (broad s, 1, methine H), 4.1 (broad s, 1, OH), 1.7–3.0 (m, 6, $CH_2CH_2CH_2$), 1.92 (s, 3, CH_3S).

Anal. Calcd for $C_{12}H_{16}O_2S$: C, 64.27; H, 7.19; S, 14.26. Found: C, 64.56; H, 7.29; S, 14.00.

1,2-Octanedione (5).—Starting from β-keto sulfoxide **1a**, procedure B gave a 79% yield of 1-methylthio-1-octanol-2-one (**4a**) as an oil (solidifying on refrigeration) which was subjected directly to vacuum distillation through a short Vigreux column. The α-keto aldehyde **5** was obtained as a bright yellow volatile fraction: bp 38–42° (0.8 mm); yield 1.1 g (38%); nmr ($CDCl_3$) δ 9.23 (s, 1, CHO), 2.71 (t, 2, CH_2CO), 0.8–2.0 (m, 11, remaining protons). The hemithioacetal **4a** was sufficiently pure to be used directly in subsequent reactions.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.63; H, 10.14. Found: C, 67.57; H, 9.92.

2-Amino-6-*n*-hexyl-4-hydroxypteridine (2a) (Procedure C).—A mixture of β-keto sulfoxide 1a (20 g, 0.1 mol), 2,4,5-triamino-6-hydroxypyrimidine sulfate monohydrate (26 g, 0.1 mol), and NaOAc (16 g, 0.2 mol) in glacial AcOH (600 ml) was stirred at room temperature for 0.5 hr and then under reflux for 1 hr. Evolved methyl mercaptan was absorbed by passage through concentrated NaOH. Cooling and filtration gave a yellow solid, which was washed with H_2O, EtOH, and Et_2O. A single crystallization of this solid (12 g) from 80% formic acid[23] yielded 3.6 g (15%) of pale yellow powder: mp >360°; nmr (CF_3CO_2H) δ 9.9 (s, C-7 proton), 8.2 (s, amidinium), 3.6 (t, C-6 methylene); uv (0.1 *N* NaOH) 253 nm (ε 20,625), 363 (5935), E_{255}/E_{365} = 3.4; R_f (1) 0.88, R_f (2) 0.77, R_f (3) 0.55.

Anal. Calcd for $C_{12}H_{17}N_5O$: C, 58.28; H, 6.92; N, 28.31. Found: 58.53; H, 7.16; N, 28.57.

2-Amino-6-*n*-heptyl-4-hydroxypteridine (2b).—This compound was obtained from β-keto sulfoxide **1b** *via* procedure C: 17% yield after one crystallization from 80% formic acid; mp >360°; nmr (FSO_3H) δ 9.9 (s, C-7 proton), 7.7 (s, amidinium), 3.6 (t, C-6 methylene); uv (0.1 *N* NaOH) 253 nm (ε 21,918), 363 (6320), E_{255}/E_{365} = 3.4; R_f (3) 0.54, R_f (4) 0.85, R_f (5) 0.87.

Anal. Calcd for $C_{13}H_{19}N_5O$: C, 59.74; H, 7.32; N, 26.79. Found: C, 59.85; H, 7.22; N, 27.05.

2-Amino-4-hydroxy-6-*n*-nonylpteridine (2c).—This compound was obtained from β-keto sulfoxide **1c** *via* procedure C: 9% yield after one crystallization from 80% formic acid; mp >360°; nmr (FSO_3H) δ 9.9 (s, C-7 proton), 7.7 (s, amidinium), 3.6 (t, C-6 methylene); uv (0.1 *N* NaOH) 253 nm (ε 21,981), 362 (6170), E_{255}/E_{365} = 3.5; R_f (5) 0.94, R_f (6) 0.91.

Anal. Calcd for $C_{15}H_{23}N_5O$: C, 62.25; H, 8.01; N, 24.20. Found: C, 62.01; H, 8.00; N, 24.03.

2-Amino-6-cyclohexylmethyl-4-hydroxypteridine (2d).—This compound was obtained from β-keto sulfoxide **1d** *via* procedure C. The keto sulfoxide was prepared from ethyl cyclohexylacetate according to procedure A and was used without purification. Crystallization of a small sample of **1d** from *i*-Pr_2O–*n*-hexane yielded colorless prisms which melted on filtration at room temperature. The pteridine, mp >360°, was obtained in 9% overall yield after one crystallization from 80% formic acid: nmr (FSO_3H) δ 9.9 (s, C-7 proton), 7.8 (s, amidinium), 3.6 (d, J = 7 Hz, C-6 methylene); uv (0.1 *N* NaOH) 252 nm (ε 24,140), 363 (6794), E_{255}/E_{365} = 3.5; R_f (3) 0.52.

Anal. Calcd for $C_{13}H_{17}N_5O$: C, 60.21; H, 6.60; N, 27.00. Found: C, 60.34; H, 6.57; N, 27.06.

2-Amino-4-hydroxy-6-(2-phenylethyl)pteridine (2e).—This compound was obtained from β-keto sulfoxide **1e** *via* procedure C: 17% yield after one crystallization from 80% formic acid; mp >360°; nmr (CF_3CO_2H) δ 8.5 (s, C-7 proton), 7.1 (s, aromatic protons), 3.2 (m, CH_2CH_2);[24] uv (0.1 *N* NaOH) 254 nm (ε 23,012), 363 (6376), E_{255}/E_{365} = 3.6.

Anal. Calcd for $C_{14}H_{13}N_5O$: C, 62.91; H, 4.90; N, 26.20. Found: C, 62.66; H, 4.82; N, 25.95.

2-Amino-4-hydroxy-6-(3-phenylpropyl)pteridine (2f).—This compound was prepared from β-keto sulfoxide **1f** *via* procedure C: 14% yield after one crystallization from 80% formic acid; mp >360°; nmr (1:4 FSO_3H–CF_3CO_2H, 2 hr equilibration time) δ 9.6 (s, C-7 proton), 8.1 (s, amidinium), 7.8 (q, $J_{AB}/\delta_A - \delta_B$ = 0.35, aromatic protons), 3.5 (m, C-6 methylene);[24] uv (0.1 *N* NaOH) 254 nm (ε 21,543), 364 (6083), E_{255}/E_{365} = 3.5.

Anal. Calcd for $C_{15}H_{15}N_5O$: C, 64.04; H, 5.37; N, 24.89. Found: C, 63.90; H, 5.40; N, 24.73.

2-Amino-7-*n*-hexyl-4-hydroxypteridine (6a).—This compound was prepared from hemithioacetal **4a** (used without purification, as in the synthesis of **5**) *via* procedure C: 74% yield after one crystallization from 80% formic acid; mp >360°; nmr (1:4 FSO_3H–CF_3CO_2H) δ 9.0 (s, C-6 proton), 8.1 (s, amidinium), 3.4 (t, C-7 methylene); uv (0.1 *N* NaOH) 251 nm (ε 19,954), 355 (8505), E_{255}/E_{365} = 2.4.

Anal. Calcd for $C_{12}H_{17}N_5O$: C, 58.28; H, 6.92; N, 28.31. Found: C, 57.98; H, 6.72; N, 28.04.

2-Amino-4-hydroxy-7-(2-phenylethyl)pteridine (6b).—This compound was prepared from hemithioacetal **4b** *via* procedure C: 59% yield after one crystallization from 80% formic acid; mp >360°; nmr (1:4 FSO_3H–CF_3CO_2H, 1 hr equilibration time) δ 9.0 (s, C-6 proton), 8.2 (s, amidinium), 7.8 (q, $J_{AB}/\delta_A - \delta_B$ = 0.33, aromatic protons), 3.4 (m, CH_2CH_2);[24] uv (0.1 *N* NaOH) 252 nm (ε 20,702), 357 (8648), E_{255}/E_{365} = 2.5.

Anal. Calcd for $C_{14}H_{13}N_5O$: C, 62.91; H, 4.90; N, 26.20. Found: C, 62.99; H, 4.79; N, 26.07.

2-Amino-4-hydroxy-7-(3-phenylpropyl)pteridine (6c).—This compound was prepared from hemithioacetal **4c** *via* procedure C: 43% yield after one crystallization from 80% formic acid; mp >360°; nmr (1:4 FSO_3H–CF_3CO_2H, 45 min equilibration time) δ 9.0 (s, C-6 proton), 8.2 (s, amidinium), 7.8 (q, $J_{AB}/\delta_A - \delta_B$ = 0.35, aromatic protons), 3.4 (m, C-7 methylene);[24] uv (0.1 *N* NaOH) 252 nm (ε 18,047), 358 (7497), E_{255}/E_{365} = 2.5.

Anal. Calcd for $C_{15}H_{15}N_5O$: C, 64.04; H, 5.37; N, 24.89. Found: C, 63.80; H, 5.28; N, 24.62.

2-Amino-6-(and 7-)*n*-hexyl-4-hydroxypteridines (2a and 6a). A. *Via* Dimethyl Acetal 3.—A solution of β-keto sulfoxide **1a** (5 g, 0.026 mol) and iodine (4.1 g, 0.016 mol) in absolute MeOH (53 ml) was stirred under reflux for 90 min, cooled, and concentrated to dryness under reduced pressure. The oily residue was taken up in $CHCl_3$ (50 ml) and excess iodine was destroyed by shaking with saturated sodium thiosulfate (2 × 50 ml). Drying and solvent evaporation gave 4.5 g (91%) of the dimethyl acetal **3** as a clear, amber-colored liquid: nmr ($CDCl_3$) δ 4.4 (s, 1, methine H), 3.4 (s, 6, CH_3O), 2.3–2.7 (m, 4, CH_2CO), 0.7–2.7 (m, 11, remaining protons). Without further purification, **3** was allowed

(23) Control experiments with mixtures of 6 and 7 isomers indicated that crystallization from 80% formic acid could not effect isomer separation and was not selectively destructive to the 7 isomer. Hence, isolation of 6 isomer as the sole product does not seem to be an experimental artifact. Rather, low material recovery during recrystallization apparently results from the fact that much of the crude solid filtered from the original reaction mixture consists of compounds which are soluble in 80% formic acid and are not pteridines.

(24) Spectra taken in freshly prepared 1:4 FSO_3H–CF_3CO_2H solutions contained prominent singlets at δ 8.6 and 7.3 which diminished rapidly on standing. Although it is possible, as one of the referees has suggested, that this is a consequence of covalent solvation, this phenomenon was observed only with the aralkyl derivatives. Nmr spectra of the alkyl-substituted pteridines did not exhibit a time-dependent character.

to react with 2,4,5-triamino-6-hydroxypyrimidine sulfate according to procedure C. The product obtained after one crystallization from 80% formic acid (1.7 g, 23%, mp >360°) was a mixture of pteridines **2a** and **6a**: uv (0.1 *N* NaOH) E_{255}/E_{365} = 3.3; nmr (1:4 FSO_3H–CF_3CO_2H) δ 9.7 and 9.0 (C-7 and C-6 protons, relative peak areas *ca.* 8:1). The spectral data indicate the 7 isomer **6a** to be present to the extent of 10–15%.

B. *Via* **Keto Aldehyde 5.**—Treatment of 1,2-octanedione (**5**) with 2,4,5-triamino-6-hydroxypyrimidine sulfate according to procedure C gave a mixture of **2a** and **6a**: uv (0.1 *N* NaOH) E_{255}/E_{365} = 3.1; nmr (1:4 FSO_3H–CF_3CO_2H) δ 9.7 and 9.0 (C-7 and C-6 protons, relative peak areas *ca.* 3:2).

Oxidation Experiments.—Pteridines **2a**, **2c**, **2d**, and **6a** were oxidized with $KMnO_4$ according to the following typical procedure. A solution of the pteridine (0.1 g) in 0.1 *N* NaOH (20 ml) was heated to 70° on the steam bath and treated dropwise with 5% $KMnO_4$ (10 ml) over a 5-hr period. The mixture was kept at 70° overnight and excess oxidant was destroyed by adding a few drops of 50% $NaHSO_3$. Filtration through Celite and acidification of the yellow filtrate to pH 2 with 2 *N* HCl afforded a fine yellow solid which was collected by centrifugation, washed with H_2O, and dried: yield 0.04 g. On the basis of uv spectral comparison with authentic samples,[6] the product obtained from pteridines **2a**, **2c**, and **2d** was identified as 2-amino-4-hydroxypteridine-6-carboxylic acid, uv (0.1 *N* NaOH) 262, 364 nm. The product derived from pteridine **6a**, on the other hand, was identified as 2-amino-4-hydroxypteridine-7-carboxylic acid, uv (0.1 *N* NaOH) 266, 372 nm. Ir spectra (KCl) of the two acids were clearly distinguishable and were in accord with published curves.[25]

Registry No.—**1a**, 39276-30-6; **1b**, 39267-31-7; **1c**, 13133-44-3; **1d**, 39267-33-9; **1e**, 30780-46-2; **1f**, 39267-35-1; **2a**, 39267-36-2; **2b**, 39267-37-3; **2c**, 39267-38-4; **2d**, 39267-39-5; **2e**, 4215-03-6; **2f**, 31419-67-7; **3**, 6956-55-4; **4a**, 39267-67-9; **4b**, 39267-68-0; **4c**, 39267-69-1; **5**, 2363-86-2; **6a**, 39267-71-5; **6b**, 39267-72-6; **6c**, 39267-73-7; ethyl *n*-heptanoate, 106-30-9; ethyl *n*-octanoate, 106-32-1; methyl hydrocinnamate, 103-25-3; methyl 4-phenylbutyrate, 2046-17-5; 2,4,5-triamino-6-hydroxypyrimidine sulfate, 39267-74-8.

(25) C. J. Pouchert, "The Aldrich Library of Infrared Spectra," Aldrich Chemical Co., Inc., 1970, p 1034, spectra A and B.

Solvolyses of 6-Substituted *trans*-2α-Decalyl Tosylates. Remote Inductive Effects and Their Solvent Effects[1]

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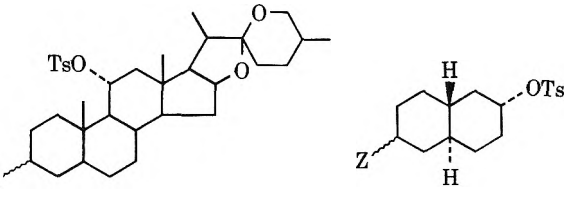
A series of 6-substituted *trans*-2α-decalyl tosylates was solvolyzed in trifluoroacetic acid, acetic acid, and ethanol. The relative rates of trifluoroacetolysis of the parent H, 6(eq)-CH_3O, 6(ax)-CH_3O, 6(eq)-C_6H_5, 6(ax)-C_6H_5, 6(eq)-Cl, 6(ax)-Cl, 6(eq)-CN, 6(ax)-CN, 6(eq)-CO_2CH_3, and 6-keto derivatives at 50° were 1.00, 1.25×10^{-1}, 9.85×10^{-2}, 4.58×10^{-1}, 6.23×10^{-1}, 1.33×10^{-1}, 2.22×10^{-1}, 5.49×10^{-2}, 4.04×10^{-2}, 1.50×10^{-1}, and 1.57×10^{-2}, respectively. Those of acetolysis were 1.00, 4.50×10^{-1}, 3.58×10^{-1}, 5.76×10^{-1}, 5.19×10^{-1}, 3.16×10^{-1}, 2.49×10^{-1}, 2.96×10^{-1}, 1.59×10^{-1}, 5.88×10^{-1}, and 1.49×10^{-1}, respectively. Those of ethanolysis were 1.00, 7.91×10^{-1}, 6.68×10^{-1}, 9.60×10^{-1}, 8.11×10^{-1}, 6.35×10^{-1}, 5.77×10^{-1}, 5.43×10^{-1}, 3.95×10^{-1}, 7.80×10^{-1}, and 6.28×10^{-1}, respectively. The acetolyses gave mainly a mixture of the Δ^1 and Δ^2 olefins and the inverted 2β-acetates with the minor retained 2α-acetate. Satisfactorily linear correlations were obtained by treatment of the rate data with the Hammett–Taft equation. The ρ^* values obtained for all the tosylates vary with solvent: −4.47 in trifluoroacetolysis, −2.05 in acetolysis, and −0.867 in ethanolysis. These results are explained in terms of remote inductive effects operating between the C_6 substituents and the C_2 reaction center. Plotting values for only the 6(eq) compounds and the 6(ax) compounds, respectively, yields significantly different ρ^* values: in acetolysis, −1.98 for eq and −2.63 for ax; in ethanolysis, −0.735 for eq and −1.30 for ax. The difference is explained in terms of a dipole–dipole interaction acting through the field between the C_6 substituents and the reaction site.

Investigation of remote substituent effects provides much useful information on the structural influence on chemical reactivity, and steroidal compounds have provided some suitable model systems for such investigation.[2-7] The significant factors governing the effects have been suggested by several groups and may be classified as (1) inductive effects, (2) electrostatic field effects, and (3) conformational transmission.[2,5,7] In a previous paper,[4] we demonstrated that the rate of acetolysis of A-ring substituted A/B-*trans*- and -*cis*-11α-*p*-toluenesulfonyloxy sapogenin derivatives decreases as the A-ring substituent becomes increasingly electronegative, and that the main cause of the rate variation is the transmission of inductive effects of the A-ring substituents through the carbon–carbon chains composing the sapogenin molecules. However, the concept of long-range inductive effects is a matter of considerable argument to the organic chemist, who traditionally expects to find significant inductive effects operating over short ranges only.[8] Our previous results have been accepted as important in connection with this argument.[2,5-7] We have therefore undertaken a study of the solvolysis of C_6-substituted



(1) Presented in part at the 23rd Symposium on Organic Reaction Mechanisms, Kobe, Japan, Oct 3, 1972.

(2) D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier, Amsterdam, 1968, pp 16–20 and 234–235.

(3) D. H. R. Barton, "Theoretical Organic Chemistry, The Kekule Symposium," Butterworths, London, 1959, p 127.

(4) K. Takeda, H. Tanida, and K. Horiki, *J. Org. Chem.*, **31**, 734 (1966).

(5) R. T. Blickenstaff and K. Sophasan, *Tetrahedron*, **28**, 1945 (1972), and references cited therein.

(6) (a) R. Baker and J. Hudec, *Chem. Commun.*, 479 (1967); (b) R. Baker and K. L. Rabone, *J. Chem. Soc. B*, 1598 (1970).

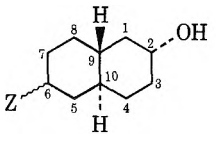
(7) D. N. Jones and R. Grayshan, *J. Chem. Soc. C*, 2421 (1970).

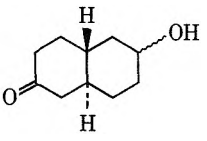
(8) For example, E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, pp 200–209.

trans-2α-decalyl (*trans,cis*-2-decalyl) tosylates[9] in trifluoroacetic acid, acetic acid, and ethanol. The decalin molecule is much simpler in structure than the sapogenin system and offers little possibility for the bending of aliphatic chains and the rotation about carbon–carbon bonds. It is therefore unlikely that the steric relationship between a polar substituent and the reaction center will change during a reaction. In addition, a structural similarity exists between both the systems; the same number of carbon atoms connect the reaction center and the substituent by the shortest carbon path in both systems. Trifluoroacetic acid has been shown to be a favorable solvent for the demonstration of inductive effect.[10]

Results

Preparations.—The preparation of series of parent and 6-substituted *trans*-decalin-2α-ols (**1**–**10**) from 2α(e)- and 2β(a)-hydroxy-*trans*-6-decalones (**11e**-OH and **11a**-OH)[11] was described in a previous paper,[12]





1, Z = H **2**, Z = eq-CH_3O **11e**-OH, eq-OH
3, Z = ax-CH_3O **4**, Z = eq-C_6H_5 **11a**-OH, ax-OH
5, Z = ax-C_6H_5 **6**, Z = eq-Cl
7, Z = ax-Cl **8**, Z = eq-CN
9, Z = ax-CN **10**, Z = eq-CO_2CH_3

which also reported the nmr spectral parameters, infrared hydroxy stretching frequencies, vpc behaviors of the alcohols, and other physical properties. Each of the compounds (**1**–**10**) used in the present study was shown by vpc to be over 99.0% pure. Treatment with *p*-toluenesulfonyl chloride in pyridine converted **1**–**10** into the tosylates (**1**-OTs–**10**-OTs), whose nmr spectral parameters and other physical constants are given in the Experimental Section.

Rates.—Acetolysis and trifluoroacetolysis were done in buffered media (in the presence of 1.1 equiv of sodium acetate or sodium trifluoroacetate), but ethanolysis was carried out without addition of base. The rates of acetolysis and ethanolysis were determined by standard procedure[13] using a potentiometer. Infinity titers corresponded to theoretical values. In each experiment the reaction was followed to 80% completion. Good first-order kinetics were observed in all runs. The rates of trifluoroacetolysis were measured by a modification of the spectrophotometric method advanced by Peterson and coworkers.[14] The samples were quenched in methanol and the decrease in the ultraviolet absorption maximum at 273.2 mμ was followed until 50% completion of the reaction. The measurement at infinity, however, did not exhibit absorbance corresponding to the theoretical values. Therefore, tosylate remaining at any time was calculated according to 1–3, and the rate constant was

$$A = c_{OTs} \cdot \epsilon_{OTs} + c_{PS} \cdot \epsilon_{PS} \quad (1)$$

$$c^{\circ}_{OTs} = c_{OTs} + c_{PS} \quad (2)$$

$$c_{OTs} = \frac{A - c^{\circ}_{OTs} \cdot \epsilon_{PS}}{\epsilon_{OTs} - \epsilon_{PS}} \quad (3)$$

obtained by determination of the slope of a straight line obtained by plotting ln c_{OTs} against time.

Here A is the absorbance at 273.2 mμ of an actual sample, c°_{OTs} is the initial concentration (moles/liter) of tosylate, c_{OTs} and c_{PS} are the concentrations of tosylate and *p*-toluenesulfonic acid, respectively, and ϵ_{OTs} and ϵ_{PS} are the molar extinction coefficients at 273.2 mμ of tosylate and *p*-toluenesulfonic acid, respectively.

The first-order rate constants were calculated by the least-squares method with a FACOM 270-20 computer, the correlation coefficients of all the plots being 0.999 ± 0.001. The rate constants and activation parameters thus obtained in trifluoroacetolysis, acetolysis, and ethanolysis are listed in Table I. For comparison of reactivities, the relative rate at 50.0° were calculated taking the rate for the parent compound as unity. The acetolysis rate of **1e**-OTs has been determined by several workers. Moritani, *et al.*,[15] reported by a titration method rate constants of 52.2 × 10^{-5} sec^{-1} at 104.50°, 11.7 × 10^{-5} at 90.09°, and 1.95 × 10^{-5} at 75.07° with $\Delta H^{\pm}$ of 28.5 kcal mol^{-1} and $\Delta S^{\pm}$ of 1.6 eu, in which the concentration of the tosylate was 17.8 mM. Baker and Rabone[6b] reported by an uv spectrometric method rate constants of 2.18 × 10^{-5} sec^{-1} at 75.0° and 31.1 × 10^{-5} at 100.0° with $\Delta H^{\pm}$ of 26.8 kcal mol^{-1} and $\Delta S^{\pm}$ of −3.4 eu, in which the concentration of the tosylate was 2.5 mM. When the acetolysis was carried out in a 20 mM solution, we obtained rate constants of 3.94 × 10^{-5} sec^{-1} at 80.2°, 11.5 × 10^{-5} at 90.0°, and 35.3 × 10^{-5} at 100.0°, which are compatible with Moritani's values. Extrapolation of the observed rates in Table I and those of Moritani and Baker to 50° gives acetolysis rate constants of 13.5 × 10^{-7} sec^{-1} at the concentration of 1.0 mM, 10.2 × 10^{-7} at 2.5 mM, 7.58 × 10^{-7} at 17.8 mM, and 8.30 × 10^{-7} at 20.0 mM. These data indicate an importance of concentration dependence of the rate constants.[16] Therefore, discussion arising from comparison of the rates in Table I is based on the assumption that the major factor for the concentration dependence in a solvent (for example, molecule–molecule association) is constant among the present tosylates, *i.e.*, independent of the C_6 substituents.

Acetolysis Products.—The acetolysis products from **1e**-OTs have already been reported, together with those from its epimer *trans*-2β-decalyl tosylate.[17] Thus, **1e**-OTs produces Δ^1-octalin in 23.7%, Δ^2-octalin in 40.2%, 2α-decalyl acetate in 2.2%, 2β-decalyl acetate in 33.3%, and other minor olefins in 0.59% yield. In

(9) All the compounds used in the present study are *dl* mixtures. For convenience, only one enantiomorph is shown in figures and, according to steroid conventions, the hydrogen at C-9 is assigned as the β orientation.

(10) (a) P. E. Peterson and G. Allen, *J. Amer. Chem. Soc.*, **85**, 3608 (1963); (b) J. E. Nordlander and W. G. Deadman, *ibid.*, **90**, 1590 (1968); (c) W. G. Dauben and J. L. Chitwood, *ibid.*, **90**, 6876 (1968).

(11) R. L. Clarke and C. M. Martin, *J. Amer. Chem. Soc.*, **81**, 5716 (1959).

(12) (a) K. Takeda and S. Yamamoto, *Chem. Pharm. Bull.*, **20**, 314 (1972); (b) *ibid.*, **20**, 1125 (1972).

(13) S. Winstein, C. Hanson, and E. Grunwald, *J. Amer. Chem. Soc.*, **70**, 812 (1948); S. Winstein, E. Grunwald, and L. L. Ingraham, *ibid.*, **70**, 821 (1948).

(14) P. E. Peterson, R. E. Kelly, Jr., R. Belloli, and K. A. Sipp, *J. Amer. Chem. Soc.*, **87**, 5169 (1965).

(15) I. Moritani, S. Nishida, and M. Murakami, *J. Amer. Chem. Soc.*, **81**, 3420 (1959).

(16) A referee suggested the importance of molecule–molecule association for this dependence.

(17) N. C. G. Campbell, D. M. Muir, R. R. Hill, J. H. Parish, R. M. Southam, and M. C. Whiting, *J. Chem. Soc. B*, 355 (1968).

the present study, the 6-methoxyl epimers (**2e**- and **3e**-OTs), the 6-chloro epimers (**6e**- and **7e**-OTs), and the keto tosylate (**11e**-OTs) were solvolyzed in glacial acetic acid containing 10% excess sodium acetate at 100.0°. Total yields of the products, determined by vpc, were roughly quantitative. In all cases, formation of the Δ^1- and Δ^2-olefinic mixture was observed in more than 50% yield, and the substitution products were mainly composed of the acetates of inverted configuration (the β acetates). For example, **2e**-OTs gave a mixture of the Δ^1-octalin and the Δ^2-octalin in 58.0% yield, the 2α-decalyl acetate in 2.1% yield, and the 2β-acetate in 32.8% yield. The products from the other tosylates are described in the Experimental Section. It is seen that substituent effects on product composition are not significant.

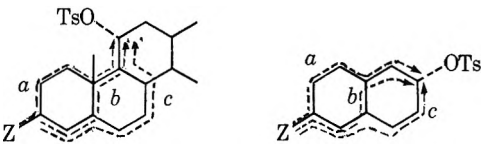
Discussion

The present compounds are conformationally fixed equatorial cyclohexyl derivatives. Cyclohexyl tosylate acetolyzes at 50° with a rate constant of 0.19×10^{-5} sec^{-1}, a $\Delta H^{\pm}$ of 28.1 kcal mol^{-1}, and a $\Delta S^{\pm}$ of 1.8 eu. *trans*-4-*tert*-Butylcyclohexyl tosylate with a fixed equatorial conformation acetolyzes at 50° with a rate constant of 0.17×10^{-5} sec^{-1}, a $\Delta H^{\pm}$ of 28.1 kcal mol^{-1}, and a $\Delta S^{\pm}$ of 1.8 eu.[18,19] Acetolysis of the present **1e**-OTs proceeds at 50° with a rate constant of 0.135×10^{-5} sec^{-1}, a $\Delta H^{\pm}$ of 26.7 kcal mol^{-1}, and a $\Delta S^{\pm}$ of −2.8 eu.[20] It has been suggested that cleavage of the secondary C–OTs in solvolysis can occur with either solvent (k_s) or hydride (k_Δ) assistance and that the two pathways by k_s and k_Δ are discrete and in competition with one another.[21] As the degree of assistance decreases to zero with the right substrate structure and solvent, k_Δ or k_s approaches k_c (anchimerically and nucleophilically unassisted process).[22] Then the ratio k_s/k_c is a measure of the degree of nucleophilic solvent participation in the absence of anchimeric assistance; when no such solvent participation is present $k_s/k_c = 1$.[21c] We have treated the rate constants of **1e**-OTs in acetic and trifluoroacetic acids with reference to those for 2-adamantyl tosylate as proposed by Schleyer, *et al.*,[21] to get a minimal measure of nucleophilic solvent assistance to ionization. Assistance factors in acetic acid $(k_s/k_c)_{HOAc}$ thus derived are 48 for **1e**-OTs[23] and 35 for cyclohexyl.[24] Therefore, the values of rates, activation parameters, and solvent assistance of the above compounds are comparable to one another.

It is seen in Table I that the introduction of an electronegative substituent into the C_6 position decreases the solvolysis rates and, further, the magnitude of the decrease increases going from ethanol to acetic acid to trifluoroacetic acid. For example, the introduction of an α-cyano group drops the relative rate to 4.04×10^{-2} in trifluoroacetic acid, 1.59×10^{-1} in acetic acid, and 3.95×10^{-1} in ethanol. The effects of carbonyl substitution are larger; the relative rates of **11e**-OTs are 1.57×10^{-2} in trifluoroacetic acid, 1.49×10^{-1} in acetic acid, and 6.28×10^{-1} in ethanol. In the previous paper[4] we observed an analogous decrease in the acetolysis rates of 11α-*p*-toluenesulfonyloxy steroidal sapogenins with introduction of the C_3 substituents, although solvent effects upon the rate variation were not investigated there. The method used to correlate the substituent effects with the acetolysis rates was based on the Hammett–Taft approach.[25,26] The rate-retarding effects of substituents were calculated from Taft substituent constants (σ^*) on the assumption that the inductive effects would be transmitted to the reaction center through all possible bond paths in the molecule. The observed effect would correspond to a summation for all possible paths (the multiple-path treatment). It was further assumed, in common with the normal Taft treatment, that the effect of any substituent would be attenuated by each bond of the intervening carbon chain. The net effect of a polar substituent was then calculated from the expression

$$\Sigma\sigma_t^* = \sigma^* [a^l + b^m + c^n + \cdots\cdots\cdots]$$

where a, b, $c\cdots$ are the attenuation factors appropriate to each bond path and l, m, $n\cdots$ are the numbers of unit groups comprising the bond path; 0.500 for one



methylene and 0.508 for one ethylene were used as the attenuation factors. The ρ^* value of −3.3 obtained from the sapogenin acetolysis is close to the value of −3.49 reported for the acetolysis of substituted cyclohexyl tosylates.[28] The close ρ^* value of the sapogenin, obtained in spite of the increased separation between the substituent and the reaction center, is a result of the higher efficiency of the transmission of polar effects through the multiple pathways (there is a mutual cancelling out of the effects of increased separation and higher efficiency).

For the Hammett–Taft treatments of the present rates, $\Sigma\sigma_t^*$ was calculated as −0.0375 for the parent compound (**1**), +0.0975 for the CH_3O compounds (**2** and **3**), +0.0403 for the phenyl compounds (**4** and **5**), +0.197 for the Cl compounds (**6** and **7**), +0.244 for the CN compounds (**8** and **9**), +0.188 for the $COOCH_3$ compound (**10**), and +0.309 for the C=O compound (**11**). Plotting the logarithms of the relative solvolysis

(18) The rate constants were taken from J. L. Mateos, C. Perez, and H. Kwart, *Chem. Commun.*, 125 (1967). The $\Delta H^{\pm}$ and $\Delta S^{\pm}$ were calculated by us with a computer.

(19) The rates were also studied by S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955).

(20) When a 20 m*M* solution of the tosylate was acetolyzed, k_1, $\Delta H^{\pm}$, and $\Delta S^{\pm}$ were 0.083×10^{-5} sec^{-1}, 28.2 kcal mol^{-1}, and 0.8 eu, respectively. Refer to "Rates" in Results.

(21) (a) J. L. Fry, C. J. Lancelot, L. K. M. Lam, J. M. Harris, R. C. Bingham, D. J. Raber, R. E. Hall, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 2538 (1970); (b) J. L. Fry, J. M. Harris, R. C. Bingham, and P. v. R. Schleyer, *ibid.*, **92**, 2540 (1970); (c) P. v. R. Schleyer, J. L. Fry, L. K. M. Lam, and C. J. Lancelot, *ibid.*, **92**, 2542 (1970).

(22) (a) S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1958); (b) footnote 2, 3, in ref 21c.

(23) The value was 34 for *trans*-2β-decalyl tosylate. The solvolyses of this compound and some related compounds will be described in a detail in a subsequent paper.

(24) Cited from J. E. Nordlander and T. J. McCrary, Jr., *J. Amer. Chem. Soc.*, **94**, 5133 (1972). The value of 30 was also reported for 4,4-dimethylcyclohexyl tosylate.

(25) In some cases a logical estimation of inductive effects of substituents was achieved by application of the Hammett–Taft relationship, $\log k/k_0 = \rho^*\sigma^*$.[10a,27,28]

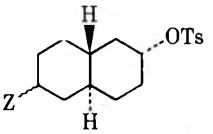
(26) Application of this method to other steroid systems to test its generality was suggested by Kirk and Hartshorn. Refer to ref 2.

(27) P. E. Peterson, *Tetrahedron Lett.*, 181 (1963).

(28) A. Streitwieser, Jr., *J. Amer. Chem. Soc.*, **78**, 4935 (1956).

TABLE I

SOLVOLYSIS RATES AND ACTIVATION PARAMETERS[a-c]



Compd (Subst., Z)	Trifluoroacetolysis Temp., °C	Trifluoroacetolysis k_1, sec^{-1}	Acetolysis Temp, °C	Acetolysis k_1, sec^{-1}	Ethanolysis Temp, °C	Ethanolysis k_1, sec^{-1}
	15.0	$(3.32 \pm 0.03) \times 10^{-5}$	80.2	$(5.19 \pm 0.12) \times 10^{-5}$	85.3	$(3.80 \pm 0.08) \times 10^{-5}$
	30.0	$(2.21 \pm 0.04) \times 10^{-4}$	95.0	$(2.52 \pm 0.25) \times 10^{-4}$	100.0	$(1.64 \pm 0.06) \times 10^{-4}$
1e-OTs	40.0	$(6.84 \pm 0.10) \times 10^{-4}$	110.3	$(1.12 \pm 0.05) \times 10^{-3}$	115.0	$(6.16 \pm 0.33) \times 10^{-4}$
(H)	50.0[d]	2.04×10^{-3}	50.0[d]	1.35×10^{-6}	50.0[d]	7.26×10^{-7}
	Rel rate	1.00	Rel rate	1.00	Rel rate	1.00
	$\Delta H^{\pm}$	21.2 ± 0.2	$\Delta H^{\pm}$	26.7 ± 0.1	$\Delta H^{\pm}$	25.2 ± 0.3
	$\Delta S^{\pm}$	-5.5 ± 0.6	$\Delta S^{\pm}$	-2.8 ± 0.2	$\Delta S^{\pm}$	8.8 ± 0.8
	30.0	$(2.52 \pm 0.02) \times 10^{-5}$	80.1	$(2.89 \pm 0.18) \times 10^{-5}$	85.2	$(3.02 \pm 0.04) \times 10^{-5}$
	40.0	$(8.05 \pm 0.09) \times 10^{-5}$	94.5	$(1.45 \pm 0.06) \times 10^{-4}$	100.0	$(1.33 \pm 0.03) \times 10^{-4}$
2e-OTs	55.0	$(4.45 \pm 0.04) \times 10^{-4}$	110.1	$(7.44 \pm 0.51) \times 10^{-4}$	115.0	$(5.00 \pm 0.29) \times 10^{-4}$
(eq-CH_3O)	50.0[d]	2.56×10^{-4}	50.0[d]	6.08×10^{-7}	50.0[d]	5.74×10^{-7}
	Rel rate	1.25×10^{-1}	Rel rate	4.50×10^{-1}	Rel rate	7.91×10^{-1}
	$\Delta H^{\pm}$	22.1 ± 0.4	$\Delta H^{\pm}$	28.4 ± 0.1	$\Delta H^{\pm}$	25.3 ± 0.4
	$\Delta S^{\pm}$	-6.7 ± 1.2	$\Delta S^{\pm}$	0.7 ± 0.3	$\Delta S^{\pm}$	-9.0 ± 1.0
	30.0	$(1.98 \pm 0.05) \times 10^{-5}$	84.8	$(3.63 \pm 0.09) \times 10^{-5}$	85.2	$(2.34 \pm 0.06) \times 10^{-5}$
	40.0	$(6.58 \pm 0.15) \times 10^{-5}$	100.4	$(1.95 \pm 0.06) \times 10^{-4}$	100.1	$(9.98 \pm 0.05) \times 10^{-5}$
3e-OTs	55.0	$(3.42 \pm 0.05) \times 10^{-4}$	115.0	$(8.29 \pm 0.49) \times 10^{-4}$	115.0	$(3.64 \pm 0.02) \times 10^{-4}$
(ax-CH_3O)	50.0[d]	2.01×10^{-4}	50.0[d]	4.83×10^{-7}	50.0[d]	4.85×10^{-7}
	Rel rate	9.85×10^{-2}	Rel rate	3.58×10^{-1}	Rel rate	6.68×10^{-1}
	$\Delta H^{\pm}$	21.9 ± 0.1	$\Delta H^{\pm}$	27.9 ± 0.03	$\Delta H^{\pm}$	24.7 ± 0.3
	$\Delta S^{\pm}$	-7.9 ± 0.2	$\Delta S^{\pm}$	-1.4 ± 0.1	$\Delta S^{\pm}$	-11 ± 1
	20.0	$(2.74 \pm 0.06) \times 10^{-5}$	80.2	$(3.33 \pm 0.07) \times 10^{-5}$	85.2	$(3.51 \pm 0.09) \times 10^{-5}$
	35.0	$(1.73 \pm 0.06) \times 10^{-4}$	95.0	$(1.72 \pm 0.05) \times 10^{-4}$	100.0	$(1.51 \pm 0.03) \times 10^{-4}$
4e-OTs	50.1	$(9.48 \pm 0.36) \times 10^{-4}$	110.2	$(7.83 \pm 0.36) \times 10^{-4}$	115.0	$(5.63 \pm 0.16) \times 10^{-4}$
(eq-C_6H_5)	50.0[d]	9.35×10^{-4}	50.0[d]	7.78×10^{-7}	50.0[d]	6.97×10^{-7}
	Rel rate	4.58×10^{-1}	Rel rate	5.76×10^{-1}	Rel rate	9.60×10^{-1}
	$\Delta H^{\pm}$	21.6 ± 0.1	$\Delta H^{\pm}$	27.6 ± 0.2	$\Delta H^{\pm}$	25.0 ± 0.3
	$\Delta S^{\pm}$	-5.8 ± 0.2	$\Delta S^{\pm}$	-1.2 ± 0.6	$\Delta S^{\pm}$	-9.5 ± 0.8
	15.0	$(2.07 \pm 0.08) \times 10^{-5}$	85.0	$(5.13 \pm 0.17) \times 10^{-5}$	85.3	$(2.88 \pm 0.11) \times 10^{-5}$
	30.0	$(1.34 \pm 0.03) \times 10^{-4}$	100.0	$(2.59 \pm 0.06) \times 10^{-4}$	100.0	$(1.24 \pm 0.03) \times 10^{-4}$
5e-OTs	45.0	$(7.47 \pm 0.05) \times 10^{-4}$	115.0	$(1.11 \pm 0.09) \times 10^{-3}$	115.0	$(4.47 \pm 0.06) \times 10^{-4}$
(ax-C_6H_5)	50.0[d]	1.27×10^{-3}	50.0[d]	7.01×10^{-7}	50.0[d]	5.89×10^{-7}
	Rel rate	6.23×10^{-1}	Rel rate	5.19×10^{-1}	Rel rate	8.11×10^{-1}
	$\Delta H^{\pm}$	21.2 ± 0.1	$\Delta H^{\pm}$	27.6 ± 0.2	$\Delta H^{\pm}$	24.8 ± 0.5
	$\Delta S^{\pm}$	-6.4 ± 0.3	$\Delta S^{\pm}$	-1.5 ± 0.6	$\Delta S^{\pm}$	-10.5 ± 1.4
	30.0	$(2.70 \pm 0.05) \times 10^{-5}$	85.0	$(3.23 \pm 0.12) \times 10^{-5}$	85.2	$(2.37 \pm 0.07) \times 10^{-5}$
	45.0	$(1.56 \pm 0.02) \times 10^{-4}$	100.0	$(1.67 \pm 0.07) \times 10^{-4}$	100.0	$(1.03 \pm 0.03) \times 10^{-4}$
6e-OTs	60.0	$(7.79 \pm 0.16) \times 10^{-4}$	115.1	$(7.24 \pm 0.37) \times 10^{-4}$	115.0	$(3.86 \pm 0.28) \times 10^{-4}$
(eq-Cl)	50.0[d]	2.71×10^{-4}	50.0[d]	4.27×10^{-7}	50.0[d]	4.61×10^{-7}
	Rel rate	1.33×10^{-1}	Rel rate	3.16×10^{-1}	Rel rate	6.35×10^{-1}
	$\Delta H^{\pm}$	21.9 ± 0.04	$\Delta H^{\pm}$	27.8 ± 0.3	$\Delta H^{\pm}$	25.1 ± 0.3
	$\Delta S^{\pm}$	-7.4 ± 0.1	$\Delta S^{\pm}$	-1.8 ± 0.9	$\Delta S^{\pm}$	-9.9 ± 0.8
	30.0	$(4.53 \pm 0.15) \times 10^{-5}$	85.0	$(2.77 \pm 0.23) \times 10^{-5}$	90.0	$(3.05 \pm 0.07) \times 10^{-5}$
	45.0	$(2.66 \pm 0.32) \times 10^{-4}$	100.0	$(1.39 \pm 0.10) \times 10^{-4}$	105.0	$(1.26 \pm 0.02) \times 10^{-4}$
7e-OTs	60.0	$(1.28 \pm 0.52) \times 10^{-3}$	115.2	$(6.59 \pm 0.48) \times 10^{-4}$	120.0	$(4.35 \pm 0.13) \times 10^{-4}$
(ax-Cl)	50.0[d]	4.53×10^{-4}	50.0[d]	3.36×10^{-7}	50.0[d]	4.19×10^{-7}
	Rel rate	2.22×10^{-1}	Rel rate	2.49×10^{-1}	Rel rate	5.77×10^{-1}
	$\Delta H^{\pm}$	21.7 ± 0.2	$\Delta H^{\pm}$	28.3 ± 0.3	$\Delta H^{\pm}$	24.4 ± 0.4
	$\Delta S^{\pm}$	-6.8 ± 0.5	$\Delta S^{\pm}$	-0.9 ± 0.7	$\Delta S^{\pm}$	-12.4 ± 1.1
	40.0	$(3.46 \pm 0.33) \times 10^{-5}$	89.7	$(5.05 \pm 0.09) \times 10^{-5}$	85.2	$(2.15 \pm 0.04) \times 10^{-5}$
	55.0	$(1.96 \pm 0.04) \times 10^{-4}$	105.0	$(2.49 \pm 0.10) \times 10^{-4}$	100.0	$(9.57 \pm 0.19) \times 10^{-6}$
8e-OTs	70.0	$(9.42 \pm 0.50) \times 10^{-4}$	119.9	$(1.05 \pm 0.14) \times 10^{-3}$	115.0	$(3.65 \pm 0.23) \times 10^{-4}$
(eq-CN)	50.0[d]	1.12×10^{-4}	50.0[d]	3.99×10^{-7}	50.0[d]	3.94×10^{-7}
	Rel rate	5.49×10^{-2}	Rel rate	2.96×10^{-1}	Rel rate	5.43×10^{-1}
	$\Delta H^{\pm}$	22.9 ± 0.1	$\Delta H^{\pm}$	27.7 ± 0.02	$\Delta H^{\pm}$	25.5 ± 0.3
	$\Delta S^{\pm}$	-6.0 ± 0.2	$\Delta S^{\pm}$	-2.2 ± 0.1	$\Delta S^{\pm}$	-9.0 ± 0.9
	40.0	$(2.62 \pm 0.05) \times 10^{-5}$	89.7	$(2.75 \pm 0.05) \times 10^{-5}$	90.0	$(2.00 \pm 0.06) \times 10^{-5}$
	55.0	$(1.43 \pm 0.07) \times 10^{-4}$	105.0	$(1.37 \pm 0.06) \times 10^{-4}$	105.0	$(7.86 \pm 0.15) \times 10^{-5}$
9e-OTs	70.0	$(6.68 \pm 0.20) \times 10^{-4}$	119.9	$(5.76 \pm 0.42) \times 10^{-4}$	120.0	$(2.76 \pm 0.02) \times 10^{-4}$
(ax-CN)	50.0[d]	8.25×10^{-5}	50.0[d]	2.15×10^{-7}	50.0[d]	2.87×10^{-7}

TABLE I (*Continued*)

(Subst., Z)	Trifluoroacetolysis Temp, °C	Trifluoroacetolysis k_1, sec^{-1}	Acetolysis Temp, °C	Acetolysis k_1, sec^{-1}	Ethanolsis Temp, °C	Ethanolsis k_1, sec^{-1}
	Rel rate	4.04×10^{-2}	Rel rate	1.59×10^{-1}	Rel rate	3.95×10^{-1}
	$\Delta H^{\pm}$	22.4 ± 0.04	$\Delta H^{\pm}$	27.8 ± 0.1	$\Delta H^{\pm}$	24.1 ± 0.1
	$\Delta S^{\pm}$	-8.1 ± 0.1	$\Delta S^{\pm}$	-3.2 ± 0.1	$\Delta S^{\pm}$	-14.4 ± 0.1
	30.0	$(2.92 \pm 0.17) \times 10^{-5}$	80.2	$(3.29 \pm 0.07) \times 10^{-5}$	85.2	$(2.92 \pm 0.01) \times 10^{-5}$
	44.5	$(1.67 \pm 0.03) \times 10^{-4}$	95.0	$(1.71 \pm 0.18) \times 10^{-4}$	100.0	$(1.29 \pm 0.05) \times 10^{-4}$
10e-OTs	60.1	$(8.96 \pm 0.15) \times 10^{-4}$	110.0	$(7.42 \pm 0.31) \times 10^{-4}$	115.0	$(4.78 \pm 0.25) \times 10^{-4}$
(eq-CO_2CH_3)	50.0[d]	3.06×10^{-4}	50.0[d]	7.94×10^{-7}	50.0[c]	5.66×10^{-7}
	Rel rate	1.50×10^{-1}	Rel rate	5.88×10^{-1}	Rel rate	7.80×10^{-1}
	$\Delta H^{\pm}$	22.2 ± 0.1	$\Delta H^{\pm}$	27.4 ± 0.4	$\Delta H^{\pm}$	25.2 ± 0.5
	$\Delta S^{\pm}$	-6.1 ± 0.4	$\Delta S^{\pm}$	-1.8 ± 1.1	$\Delta S^{\pm}$	-9.3 ± 1.2
	50.0	$(3.21 \pm 0.04) \times 10^{-5}$	90.7	$(3.01 \pm 0.32) \times 10^{-5}$	90.0	$(3.18 \pm 0.05) \times 10^{-5}$
	65.0	$(1.60 \pm 0.02) \times 10^{-4}$	105.8	$(1.52 \pm 0.24) \times 10^{-4}$	105.0	$(1.25 \pm 0.01) \times 10^{-4}$
11e-OTs	80.0	$(7.10 \pm 0.08) \times 10^{-4}$	120.0	$(5.89 \pm 0.46) \times 10^{-4}$	120.0	$(4.39 \pm 0.18) \times 10^{-4}$
(=CO)	50.0[d]	3.20×10^{-5}	50.0[d]	2.01×10^{-1}	50.0[d]	4.56×10^{-7}
	Rel rate	1.57×10^{-2}	Rel rate	1.49×10^{-1}	Rel rate	6.28×10^{-1}
	$\Delta H^{\pm}$	22.7 ± 0.1	$\Delta H^{\pm}$	28.1 ± 0.3	$\Delta H^{\pm}$	24.1 ± 0.06
	$\Delta S^{\pm}$	-8.9 ± 0.2	$\Delta S^{\pm}$	-2.3 ± 0.9	$\Delta S^{\pm}$	-13.2 ± 0.1

[a] The concentrations of tosylates were 50 mM for trifluoroacetolyses and 1.0 mM for acetolyses and ethanolyses. Temperature deviation was ±0.03°. [b] Error limits for rate constants are 95% confidence limits [degree of freedom, $\phi = n - 2$ ($n = 10$)]. [c] $\Delta H^{\pm}$ and $\Delta S^{\pm}$ were calculated by the Eyring equation and their errors are standard deviations. [d] Rates at 50° were calculated from observed rates at other temperatures and used for comparison of reactivities.

rates at 50° in trifluoroacetic acid, acetic acid, and ethanol against the $\Sigma\sigma_t^*$ constants, respectively, yielded reasonably linear correlations as shown in Figures 1–5. The ρ^* values thus obtained are listed in Table II with correlation coefficients. In Table II,

TABLE II
ρ^* VALUES

Solvent	ρ^* value		No. of compound	Correlation coefficient
CF_3COOH	(A)	−4.59	7	0.948
	(B)	−4.25	5	0.853
	(C)	−4.47	11	0.894
CH_3COOH	(A)	−1.98	7	0.900
	(B)	−2.63	5	0.988
	(C)	−2.05	11	0.871
C_2H_5OH	(A)	−0.735	7	0.901
	(B)	−1.30	5	0.970
	(C)	−0.867	11	0.792

A, B, and C designate the ρ^* values determined from the rates of the C_6-equatorial compounds, the C_6-axial compounds, and both the C_6-axial and C_6-equatorial compounds, respectively. The differences among the ρ^*(A), ρ^*(B), and ρ^*(C) values in trifluoroacetic acid cannot be thought to be mathematically significant if the relationship between correlation coefficients and number of compounds is considered. However, the differences between the ρ^*(A) and ρ^*(B) values in acetic acid and ethanol are significant; the ρ^*(B) values from the axial compounds are seen to be larger than those for the equatorial compound (Figures 4 and 5).

The magnitude of ρ^* increases with solvent change from ethanol to acetic acid to trifluoroacetic acid. That the highest ρ^* is in trifluoroacetic acid is a reasonable result of the enhanced inductive effects in this solvent of low nucleophilicity. Enhancement of an electronic effect of this kind in trifluoroacetic acid has been well studied.[10a,14,29]

(29) P. E. Peterson, C. Casey, E. V. P. Tao, A. Agtarap, and G. Thompson, *J. Amer. Chem. Soc.*, **87**, 5163 (1965).

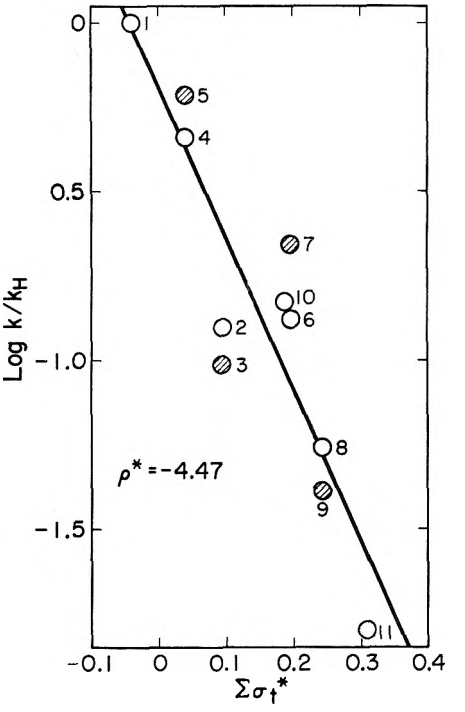


Figure 1.—$\rho^*\sigma^*$ correlation obtained from trifluoroacetolysis rates of both the C_6-axial and C_6-equatorial compounds at 50°. Points denoted by open circles refer to C_6-equatorial; those denoted by shaded circles refer to C_6-axial compounds. Numbers with circles refer to compound numbers of the tosylates in Table I.

In connection with a model for electrostatic field effects, it was of interest to us to examine the influence of the orientation of C_6 substituents on the solvolysis rates of the C_2-equatorial tosylates. The rate ratios of the tosylates bearing the C_6-axial substituent to those bearing the C_6-equatorial substituent, k_{ax}/k_{eq}, were calculated and are presented in Table III. It was observed by Noyce and Johnston[30] that 3α(a)-chloro-5α-cholestan-6α-yl tosylate solvolyzes in acetic acid

(30) (a) D. S. Noyce and G. A. Selter, *J. Org. Chem.*, **36**, 3458 (1971); (b) D. S. Noyce, B. N. Bastian, R. T. S. Lau, R. S. Monson, and B. Wiensten, *ibid.*, **34**, 1247 (1969); (c) D. S. Noyce and B. E. Johnston, *ibid.*, **34**, 1252 (1969).

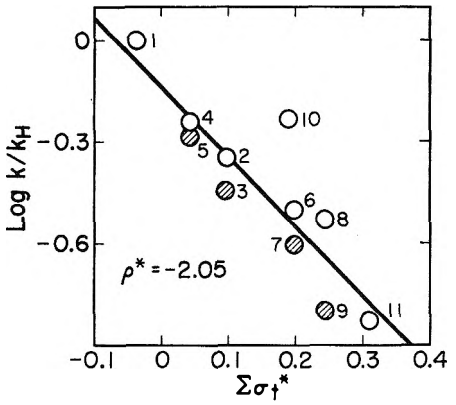


Figure 2.—$\rho^*\sigma^*$ correlation obtained from acetolysis rates of both the C_6-axial and C_6-equatorial compounds at 50° (use of points and numbers as in Figure 1).

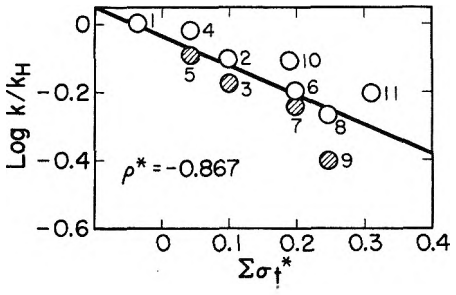


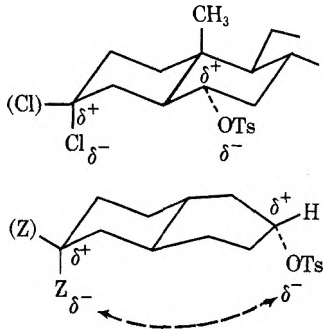
Figure 3.—$\rho^*\sigma^*$ correlation obtained from ethanolysis rates of both the C_6-axial and C_6-equatorial compounds (use of points and numbers as in Figure 1).

TABLE III

RATE RATIOS BETWEEN C_6(ax)- AND C_6(eq)-SUBSTITUTED TOSYLATES AT 50.0°

Substituent	k_{ax}/k_{eq} CF3COOH	AcOH	EtOH
CH_3O	0.785	0.794	0.845
C_6H_5	1.36	0.901	0.845
Cl	1.67	0.787	0.909
CN	0.737	0.539	0.728

faster than its 3β (equatorial) epimer; k_{ax}/k_{eq} = 1.8 at 75°. As the major factor for this,[30] they pointed out



that the negative end of the chloro dipole substituent in the more reactive 3α tosylate lies closer to the reaction center than the corresponding end in the less reactive 3β tosylate. In the present study, the C_6-(equatorial) substituted compounds are a little more reactive than the C_6-(axial) substituted compounds and the k_{ax}/k_{eq} ratios are roughly constant, being in the range of 0.7–0.9 in all three solvents, although trifluoroacetolyses of chloro- and phenyl-substituted compounds are exceptions. The inductive effect operating through

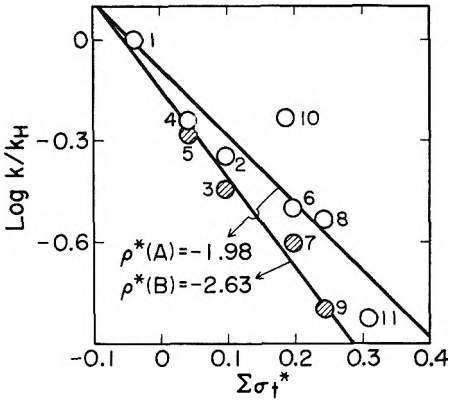


Figure 4.—Individual $\rho^*(A)\sigma^*$ and $\rho^*(B)\sigma^*$ correlations obtained from acetolysis rates of the C_6-axial and C_6-equatorial compounds (use of points and numbers as in Figure 1).

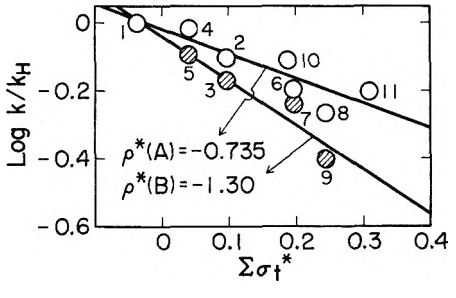


Figure 5.—Individual $\rho^*(A)\sigma^*$ and $\rho^*(B)\sigma^*$ correlations obtained from ethanolysis rates of the C_6-axial and C_6-equatorial compounds (use of points and numbers as in Figure 1).

C–C bonds cannot provide an explanation of this reactivity difference resulting from the orientation of the C_6 substituents. Inspection of molecular models indicates that the negative ends of the axial dipolar substituents lie closer to the negative end of the leaving tosyloxy group, assuming the usual half-chair conformation for the reacting ring.

We consider the reason why reactivities of the C_6 (axial) tosylates are lower than those of their equatorial counterparts is that unfavorable dipole–dipole interaction between the substituent and the leaving tosyloxy group (between the two δ^- in the picture) is greater in the axial compounds. As mentioned above, the $\rho^*(B)$ values in acetic acid and ethanol are larger than the corresponding $\rho^*(A)$ values; the rate-retarding effects of the axial substituent are greater than those of the equatorial substituents. This fact is thought to be an important indication for a field effect such as dipole–dipole interaction. The $\rho^*(B)$ value in trifluoroacetic acid is not larger than the $\rho^*(A)$ value. In this highly acidic solvent, solvation (protonation) of the negative ends of the dipoles would be very strong, rendering them incapable of interaction.

Experimental Section

Melting points were taken on a Yanagimoto melting point apparatus and are uncorrected. Nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as internal standard. Infrared spectra were measured on a Nippon Bunko DS201B spectrometer. Uv spectra were measured on a Hitachi EPS-032 and/or a Hitachi EPU-2A spectrometer. Vpc analyses were performed on a Hitachi gas chromatograph Model K53 equipped with a hydrogen flame ionization detecter using the following columns: (A) 1 m × 3 mm stainless steel column packed with Carbowax 20M 5%, (B) 2 m × 3 mm Carbowax

20M 10%, and (C) 2 m × 3 mm DEGS 10%. Nitrogen was used as a carrier gas.

2α- and 2β-hydroxy-*trans*-6-decalones (11e-OH and 11a-OH) were prepared from 6-methoxy-2-tetralol[31] by methods described in the literature.[11]

6-Substituted 2α-*trans*-decalols (1e-OH–10e-OH) were synthesized from 11e-OH or 11a-OH in accordance with methods described in the literature.[12]

General Procedure of Tosylation.—To a solution of the alcohol, whose purity (more than 99.0%) was checked by vpc analyses, in pyridine was added about 1.3–1.5 molar equiv of *p*-toluenesulfonyl chloride under ice cooling and the mixture was allowed to stand at 6–10°. Cracked ice and water were added to the reaction mixture and the resulting precipitate or mixture was extracted with ether. The ether solution was washed with chilled water, dried over sodium sulfate, evaporated, and purified by silica gel chromatography followed by recrystallization. Properties and elementary analyses of *p*-toluenesulfonates prepared in this study are summarized in Table IV. Nmr data of the C_2 and C_6 protons were used to establish the configuration of substituents and the molar extinction coefficient (ϵ) at 273.2 mμ of the tosylates was used for the trifluoroacetolysis rates.

TABLE IV

PROPERTIES, ANALYSES, AND SPECTRAL PARAMETERS OF *p*-TOLUENESULFONATES[a]

Compd	Mp, °C	Formula	Nmr in $CDCl_3$, δ[b] C_2 H	C_6 H	ϵ_{max}[c]
1e-OTs	62–63	$C_{17}H_{24}O_3S_1$	4.44 (21)		448
2e-OTs	90–91	$C_{18}H_{26}O_4S_1$	4.43 (21)	3.13 (21)	455
3e-OTs	66–67	$C_{18}H_{26}O_4S_1$	4.47 (21)	3.50 (7)	452
4e-OTs	112–113	$C_{23}H_{28}O_3S_1$	4.43 (21)	2.56 (21)	461
5e-OTs	92–94	$C_{23}H_{28}O_3S_1$	4.44 (21)	3.12 (10)	466
6e-OTs	146–147	$C_{17}H_{23}O_3S_1Cl_1$	4.43 (21)	3.80 (21)	463
7e-OTs	83–84	$C_{17}H_{23}O_3S_1Cl_1$	4.43 (21)	4.4–4.6	457
8e-OTs	157–158	$C_{18}H_{23}O_3S_1N_1$	4.42 (21)	2.4–2.5	460
9e-OTs	131–133	$C_{18}H_{23}O_3S_1N_1$	4.44 (21)	2.98 (7)	457
10e-OTs	98–99	$C_{19}H_{26}O_5S_1$	4.43 (21)	2.3–2.4	460
11e-OTs	80–82	$C_{17}H_{22}O_4S_1$	4.53 (23)		460

[a] Satisfactory analyses (±0.3% in C, H, and S) were reported for all compounds in the table: Ed. [b] Downfield from $(CH_3)_4Si$. Values in parentheses are half-height band widths in hertz. [c] Molecular extinction coefficient of λ_{max} 273.2 mμ in CH_3OH solutions, taken with a Hitachi EPU-2A spectrometer using a 10-mm cell with cap.

Kinetic Measurements in Acetic Acid and Ethanol.—Measurements of the rates of acetolyses and ethanolyses were carried out by the standard procedure.[13] Reagent grade acetic acid was heated under reflux with about 5% potassium permanganate for 10 hr, distilled, dried over phosphorus pentoxide, and then redistilled. The distilled acid was further purified by collecting the fraction boiling at 117–118° after refluxing with addition of 5% of acetic anhydride; 1% acetic anhydride was then added. Sodium acetate standard solution was made by dissolving anhydrous sodium carbonate in acetic acid and by refluxing for 5 hr with sufficient acetic anhydride to remove the water of neutralization, and its concentration was adjusted to 0.022 *M* at room temperature. Sodium acetate solution (1.1 m*M*) was diluted with the above acetic acid before use. Ethanol (99.5%) was heated under reflux with about 3% sodium metal for 2 hr and then distilled through a vacuum-jacketed column packed with glass rings. The middle fraction was collected and stored under argon.

For acetolysis, a solution of 1.0 m*M* of the tosylate in acetic acid containing 1.1 m*M* sodium acetate was prepared at room temperature. Aliquots (4.0 ml) were distributed into tubes which were sealed under nitrogen after freezing in Dry Ice–acetone. The tubes were placed in a constant-temperature bath and were successively withdrawn after appropriate intervals of time. "Infinity" tubes were removed after at least 10 half-lives and usually three were taken for each run. The contents were cooled and diluted with 10 ml of acetic acid and remaining sodium acetate was titrated with standard 0.004 *N* perchloric acid in acetic acid using a Metrohm potentiograph E336 A. Plots of log $(A_t - A_\infty)$ *vs.* time, where A_∞ and A_t are titers at infinity and at the given times, respectively, were uniformly linear. The slopes multiplied by −2.303 gave the pseudo-first-order rate constants.

Ethanolysis was carried out without addition of base. Rates were measured by the above-described technique, the concentration of tosylates being 1.0 m*M*. The tubes (4.0 ml), which were withdrawn after appropriate intervals of time, were cooled and diluted with 10 ml of 99.5% ethanol. Rates of acid formation were followed by potentiometric titration using 0.004 *N* aqueous sodium hydroxide. The rate constants were determined by the infinity titer method as in the acetolysis.

Kinetic Measurements in Trifluoroacetic Acid.—The rates of trifluoroacetolysis were measured by a modification of the spectrophotometric method advanced by Peterson and coworkers.[14] Trifluoroacetic acid (2 l.) and trifluoroacetic acid anhydride (50 ml) were refluxed for 5 hr. The solution was then distilled through a vacuum-jacketed column packed with glass rings. The middle fraction was collected and stored under argon. After distillation, 1% trifluoroacetic anhydride was added to the acid. Buffered medium was made in a volumetric flask by dissolving anhydrous sodium carbonate in the above trifluoroacetic acid, allowing it to stand for 1 day at room temperature with sufficient trifluoroacetic anhydride to remove the water of neutralization, then adjusting its concentration to 0.06 *M*. A solution of 0.05 *M* of the tosylates in trifluoroacetic acid containing 0.06 *M* sodium trifluoroacetate was prepared at 0° and aliquots (1.0 ml) were distributed into tubes which were sealed under nitrogen after freezing in Dry Ice–acetone. The tubes were placed in a constant-temperature bath and were successively withdrawn after appropriate intervals of time. The contents were cooled in a salt–ice bath. Each tube was opened, poured into a 50-ml volumetric flask, and diluted with methanol up to the mark. The absorbance of the remaining tosylate was measured at 273.2 mμ using a Hitachi EPU-2A spectrometer. In all the measurements, the spectrometer was zeroed at 285.0 mμ with the actual sample. The rate constants were determined by the plots against time of log c_{OTs}, calculated from the equations given in Results.

The validity of this method was confirmed by direct comparison with rate constants calculated by the infinity titer method for the compounds 8e-OTs, 9e-OTs, and 11e-OTs. The differences between rate constants obtained by the two methods were within 3%.

Acetolysis Products.—A solution of 0.6 mmol of the tosylate in 30 ml of acetic acid containing 0.022 *M* sodium acetate was sealed in a glass bomb under nitrogen after being frozen in Dry Ice–acetone. The bomb was then heated at 100.0° for a specified time (10–11 half-lives), calculated from the previously determined rate constant. The bomb was cooled and opened; the reaction mixture was poured into water and extracted with ether. The combined ethereal extract was washed with water, aqueous potassium carbonate, and water, dried over sodium sulfate, and evaporated. The product was analyzed by vpc and the ratio of acetate to olefin was determined by peak area measurement. The olefin and acetate fractions were then separated on a small column of silica gel (4–5 g.); elution with 2 or 3 column volumes of *n*-hexane gave the olefin fraction and further elution with ether–*n*-hexane (1:4) gave the acetate fraction. The olefin fractions were collected, dried under reduced pressure, and weighed. The acetate fractions were collected and identified with authentic samples.[12] The yields of the acetates were determined to be quantitative by vpc with internal standards. No data indicating rearranged acetates were obtained in the product analyses. The olefin fractions were shown to consist of the Δ^1 olefin and the Δ^2 olefin by nmr and mass spectra and vpc analyses. Separation of the olefins by vpc was not satisfactory on our columns. The olefin fraction from 2e-OTs showed nmr ($CDCl_3$) δ 3.18 (1 H, broad s, $W_{1/2}$ = 21 Hz, C_6-ax H), 3.35 (3 H, s, OCH_3), 5.4–5.7 (2 H, m, olefinic protons); mass spectrum *m/e* 166 (M^+). That from 3e-OTs showed nmr ($CDCl_3$) δ 3.30 (3 H, s, OCH_3), 3.52 (1 H, broad s, $W_{1/2}$ = 7 Hz, C_6-eq H), 5.4–5.7 (2 H, m, olefinic protons); mass spectrum *m/e* 166 (M^+). That from 6e-OTs showed nmr ($CDCl_3$) δ 3.90 (1 H, broad s, $W_{1/2}$ = 21 Hz, C_6-ax H), 5.4–5.7 (2 H, m, olefinic protons); mass spectrum *m/e* 170 (M^+). That from 7e-OTs showed nmr ($CDCl_3$) δ 4.53 (1 H, broad s, $W_{1/2}$ = 7 Hz, C_6-eq H), 5.4–5.7 (2 H, m, olefinic protons); mass spectrum *m/e* 170 (M^+). That from 11e-OTs showed nmr ($CDCl_3$) δ 5.5–5.7 (2 H, m, olefinic protons); mass spectrum *m/e* 150 (M^+).

Products and yields from 1e-OTs and 2e-OTs were described in Results. Products from 3e-OTs were an olefin mixture of 57.9%,

(31) W. Nagata and T. Terasawa, *Chem. Pharm. Bull.*, **9**, 267 (1961).

the 2α-acetate of 2.7%, and the 2β-acetate of 34.0%. Those from 6e-OTs were the olefin mixture of 57.1%, the 2α-acetate of 1.7%, and the 2β-acetate of 35.4%. Those from 7e-OTs were the olefin mixture of 58.1%, the 2α-acetate of 1.6%, and the 2β-acetate of 34.0%. Those from 11e-OTs were the olefin mixture of 55.2%, the 2α-acetate of 1.1%, and the 2β-acetate of 31.9%.

Registry No.—**1e**, 2529-06-8; **1e**-OTs, 19124-24-4; **2e**, 36284-21-6; **2e**-OTs, 39003-14-0; **3e**, 36126-50-8; **3e**-OTs, 39003-16-2; **4e**, 36407-90-6; **4e**-OTs, 36126-60-0; **5e**, 36126-54-2; **5e**-OTs, 39062-17-4; **6e**, 36126-58-6; **6e**-OTs, 39010-18-9; **7e**, 36284-22-7; **7e**-OTs, 39010-20-3; **8e**, 36126-73-5; **8e**-OTs, 39010-22-5; **9e**, 36126-63-3; **9e**-OTs, 39010-24-7; **10c**, 36126-75-7; **10e**-OTs, 39010-26-9; **11e**, 34824-00-5; **11e**-OTs, 36126-61-1; *p*-toluenesulfonyl chloride, 98-59-9.

The Cycloaddition of Ethylene to Acrylonitrile

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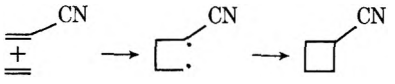
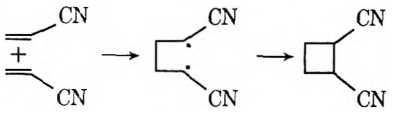
The thermal and catalyzed cycloadditions of ethylene to an acrylonitrile were investigated experimentally and theoretically. At 300–345° and 1000 atm ethylene pressure, up to 30% conversion of acrylonitrile to cyclobutanecarbonitrile were obtained. The reaction reached equilibrium under these conditions. This was shown by obtaining the thermodynamic properties of cyclobutanecarbonitrile by spectroscopic means, and calculating the free-energy change for the reaction: $\Delta F° = -21{,}500 + 45.52T$. Below 300° kinetic control occurred. A catalyst search revealed weak acceleration by nickel(0) compounds. This is the second example of cycloaddition of ethylene catalyzed by a transition metal.

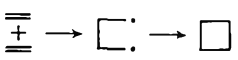
In connection with work on the synthesis and polymerization of 1-bicyclobutanecarbonitrile,[2] the need arose for a ready synthesis of cyclobutanecarbonitrile as a possible intermediate. The cycloaddition of ethylene to acrylonitrile suggested itself as such a route.



Although this reaction has not been reported previously, cyclodimerization of each of these olefins to itself is known. Coyner and Hillman[3] showed that acrylonitrile underwent cyclodimerization at 200° in 20% yield, and this reaction has subsequently received much attention in the patent literature.[4-7] The biradical mechanism was ascribed to this reaction.[3]



Recently Back and coworkers[8] carried out the thermal cyclodimerization of ethylene to cyclobutane. At



450° with a reaction time of 5–20 min, a 0.02% conversion to cyclobutane was achieved.

The results of our studies on the cycloaddition of ethylene to acrylonitrile form the basis of the present report.

Results

Thermal Cycloadditions.—The reactions were carried out in stainless steel pressure vessels at elevated temperatures. It was found necessary to work at 300–345° to obtain significant conversions to cyclobutanecarbonitrile. Ethylene, at 1000 atm pressure, was used in large excess over acrylonitrile (17:1–30:1) to form the desired cycloaddition and to minimize the competing cyclodimerization of acrylonitrile. This pressure was about optimum; use of 3000 atm led to lower decomposition temperatures and tar formation.[9] Polymer and tar formation were minimized by adding inhibitors. Best results below 300° were achieved with *p*-methoxyphenol or 2,6-di-*tert*-butylresorcinol; above 300° these inhibitors were used in conjunction with cupric salts. Addition of a little water[6] to the reaction mixtures was also beneficial in minimizing tar formation. The results are summarized in Table I. There is considerable scatter owing to experimental difficulties. However, under best conditions, up to 30% of the acrylonitrile charged can be converted to cyclobutanecarbonitrile.

Calculation of Equilibrium Constants.—It was considered important to establish whether the observed yields were limited by equilibrium or by kinetic factors. To this end we calculated the free-energy change of the cycloaddition reaction as a function of temperature, using spectroscopic methods to determine the individual free energies.

The thermodynamic properties of ethylene[10] and of acrylonitrile[11,12] as functions of temperature were already available. The heat of formation of cyclobutanecarbonitrile was also known.[13] For the variation of

(1) Address correspondence to Department of Chemistry, University of Arizona, Tucson, Arizona 85721.

(2) H. K. Hall, Jr., *Brit. Polym. J.*, in press.

(3) E. C. Coyner and W. S. Hillman, *J. Amer. Chem. Soc.*, **71**, 324 (1949).

(4) K. Sennewald, A. Goetz, and G. Kalbrath, German Patent 1,081,008 (1960) to Knapsack-Griesheim AG; *Chem. Abstr.*, **55**, 13338 (1961).

(5) French Patent 1,397,085 (1965) to Knapsack-Griesheim AG; *Chem. Abstr.*, **63**, 6885 (1965).

(6) J. D. Idol, J. L. Greene, and N. R. Gray, U. S. Patent 3,275,675 (1966) to Standard Oil Co. of Ohio; *Chem. Abstr.*, **65**, 18507 (1966).

(7) T. Sato and H. Hasmi, Japanese Patent 22,979 (1968); *Chem. Abstr.*, **70**, 57266 (1969).

(8) L. M. Quick, D. A. Knecht, and M. H. Back, *Int. J. Chem. Kinet.*, **4**, 61 (1972).

(9) A referee has suggested that cycloadditions of acrylonitrile work best in the gas phase, and that the deleterious effect of increased pressure consists of increasing the amount of liquid phase.

(10) National Bureau of Standards Circular 500 (1952).

(11) F. Halverson, R. F. Stamm and P. J. Whalen, *J. Chem. Phys.*, **16**, 808 (1948).

(12) H. L. Finke, J. F. Messerly, and S. S. Judd, *J. Chem. Thermo.*, **4**, 359 (1972).

(13) H. K. Hall, Jr., and J. H. Baldt, *J. Amer. Chem. Soc.*, **93**, 140 (1971).

TABLE I

THERMAL CYCLOADDITION OF ETHYLENE TO ACRYLONITRILE. EXPERIMENTAL RESULTS[a]

Temp, °C	Initial mmol of acrylonitrile	Concn of ethylene, mol l.$^{-1}$	Cyclobutanecarbonitrile found, mmol: 0.08 hr	0.17 hr	0.25 hr	0.5 hr	1 hr	2 hr	3 hr	4 hr
225	150	14.3			0.1–0.2					
250	900	13.6						7–8 (2 runs)		
275	300	13.3						2–7 (4 runs)	1–13 (5 runs)	3–11 (2 runs)
300	150	13.0		9	3–8 (2 runs)	5	9–21 (2 runs)	11–14 (3 runs)		
	300	13.0			13	7	5–11 (4 runs)	6–36 (4 runs)		
325	150	12.5		10–24 (8 runs)	12–26 (10 runs)	9–36 (17 runs)	19			
335	150	12.3		17–18 (2 runs)						
	300	12.3		14–47 (4 runs)		20–65 (27 runs)				
	600	12.3		20–82 (7 runs)						
345	150	12.0	11–12 (2 runs)	14–44 (13 runs)	16–33 (3 runs)	24				

[a] Conditions: Pressure vessel volume, 0.4 l.; ethylene, 1000 atm pressure at reaction temperature (concentration calculated from gas density at given pressure and temperature); water, 2 ml, added to all runs to inhibit resin formation; inhibitors below 300°, 0.15 g of 2,5-di-*tert*-butylhydroquinone or of 2,6-di-*tert*-butylcatechol; inhibitors at or above 300°, same plus 0.15 g of cupric chloride, cupric acetate, cupric bromide, or cupric fluoroborate.

thermodynamic properties of this compound with temperature, the fundamental frequencies were obtained from the work of Lord and Blackwell[14] (Table II). The important ring-puckering vibration is given as a harmonic oscillator approximation in Table II. The actual potential function, obtained by far-infrared measurements, is given by Carreira and coworkers,[15] and the energy levels are given in Blackwell's thesis.[14] From the fundamental vibrational frequencies in Table II, the variation of thermodynamic properties with temperature was calculated.[16] The harmonic oscillator approximation was used for all vibrations, for which the detailed energy levels were used. The thermodynamic properties are given as functions of temperature in Table III. Combination of the free energies leads to the free-energy change for the reaction of ethylene and acrylonitrile, $\Delta F_T^\circ = -21{,}500 + 45.52T$. The reaction is strongly favored at room temperature but is progressively disfavored at higher temperatures.

Having this relationship, we were now able to calculate the equilibrium constants for our reaction conditions (see Experimental Section for details). Table IV compares the values found for the equilibrium constant with those calculated for various temperatures. Agreement above 300° is good considering the difficult nature of the experiments, and indicates that the equilibrium has been achieved. Support for this proposal is afforded by the independence of yield with time at these temperatures, although the variation from run to run makes this somewhat tenuous.

Also, under these conditions the reaction was shown to be reversible, by heating cyclobutanecarbonitrile at 325° for 0.5 hr under 1000 atm pressure of ethylene. Acrylonitrile was present in the product, as established by gas chromatography.

TABLE II

FUNDAMENTAL VIBRATIONS FOR CYCLOBUTANECARBONITRILE

Type of vibrations	No. of contributions	Fundamental vibration frequency, cm^{-1}	Description
A′ (20)	1	138[a]	Ring puckering[a]
	1	260	Ring–CN bending
	1	518	C–CN bending
	1	588	CH_2 rocking
	1	719	CH_2 rocking
	1	748	Ring deformation
	1	887	C–CN stretching
	1	939	Ring breathing
	1	1046	Ring deformation
	1	1109	CH deformation (in plane)
	1	1250	CH_2 twist
	1	1330	CH_2 wagging
	2	1449	CH_2 deformation
	1	2239	CN stretch
	5	2950	CH_2 stretch
A″ (13)	1	176[b]	Ring–CN bending
	1	480	C–CN bending
	1	673	CH_2 rocking
	1	784	Ring deformation
	1	921	Ring deformation
	1	1109	CH deformation
	2	1212	CH_2 twisting
	2	1250	CH_2 wagging
	1	1462	CH_2 deformation
	2	2998	CH stretch

[a] Estimated from the observed far-infrared transitions as the harmonic frequency needed to represent the contribution of the ring-puckering vibration to the thermodynamic functions: R. C. Lord and C. S. Blackwell, unpublished results. [b] From far-infrared type B band (gas).

(14) C. S. Blackwell, Ph.D. Thesis, M. I. T., June 1971, Chapter 2; R. C. Lord, private communication.

(15) C. S. Blackwell, L. A. Carreira, J. R. Durig, J. M. Karriker, and R. C. Lord, *J. Chem. Phys.*, **56**, 1707 (1972).

(16) N. B. Colthup, L. H. Daly, and S. E. Wiberly, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York, N. Y., 1964, pp 463–484.

TABLE III

THERMODYNAMIC PROPERTIES OF CYCLOBUTANECARBONITRILE[a]

Temp, °K	$\frac{H_T^\circ - E_0^\circ}{T}$	H_T°	$\frac{F_T^\circ - E_0^\circ}{T}$	F_T°	S°	C_p
0	0	39.62	0	39.62	0	0
298.2	13.22	43.56	−60.10	21.69	73.32	22.37
400	16.48	46.21	−64.43	13.84	80.92	29.53
500	19.70	49.47	−68.46	5.39	88.16	35.46
600	22.75	53.27	−72.32	−3.78	95.07	40.31
700	25.55	57.50	−76.04	−13.61	101.60	44.32
800	28.11	62.11	−79.63	−24.01	107.74	47.69

[a] Assumptions: symmetry C_s, $\sigma = 1$; electronic contributions negligible; all vibrations are harmonic oscillations except ring puckering, the energy levels for which are taken directly from Table I; ring puckering angle 30°. Parameters: $I_A = 0.092132 \times 10^{-37}$ g cm^{-2}; $I_B = 0.334808 \times 10^{-37}$ g cm^{-2}; $I_C = 0.376698 \times 10^{-37}$ g cm^{-2}; mol wt, 81.110.

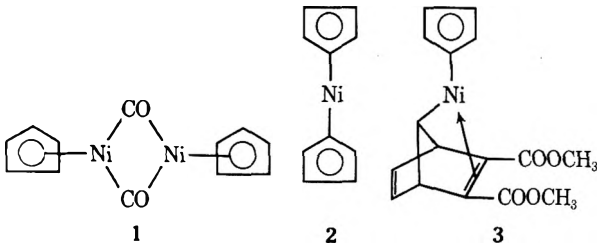
TABLE IV

COMPARISON OF CALCULATED AND FOUND EQUILIBRIUM CONSTANTS

Temp, °C	ΔF_t° kcal mol^{-1}	$10^2 K_{calcd}$, l. mol^{-1}	$10^2 K_{exptl}$, l. mol^{-1}	Ratio of exptl/calcd
345	6.6	0.49	1	2.4
335	6.1	0.66	0.7	1.0
		0.66	0.8	1.3
		0.66	0.5	0.8
325	5.6	0.89	1	1.3
				Av 1.4 ± 0.4
300	4.5	1.9	0.5	0.27
		1.9	0.4	0.19
275	3.4	4.6	0.1	0.028
250	2.4	10	0.04	0.0039
225	1.2	30	0.006	0.00019

At lower temperatures, however, where equilibrium considerations would give more cyclobutanecarbonitrile, less is actually obtained. This suggests kinetic control at these temperatures. This is supported by the fact that here the yields appear to increase with time.

Catalyzed Cycloadditions.—Our results for the thermal cycloaddition showed that, at temperatures where reasonable rates could be obtained, the equilibrium amount of cyclobutanecarbonitrile was very small. It was appropriate to look for a catalyst which, giving higher rates at lower temperatures, would allow us to use lower temperatures with accompanying higher equilibrium concentrations of the desired product. Many compounds were screened as potential catalysts. These scouting experiments were carried out under milder conditions than the shaker tubes used above, namely in sealed glass ampoules containing 1300 psi of ethylene at 250–275° for 2–4 hr. Under these conditions, no cyclobutanecarbonitrile was detectable in the absence of catalysts. Weak acceleration under these conditions was demonstrated for several organonickel complexes, including π-cyclopentadienylnickel carbonyl, nickelocene, and π-cyclopentadienyl 2,3-biscarbomethoxy-2π,5-norbornadien-7-ylnickel (Table V). Use of various solvents (THF, hexane, acetonitrile) decreased yields. The formation of cyclobutanecarbonitrile was not proved to be a truly catalytic process; perhaps it is a stoichiometric reaction of π-bonded acrylonitrile or ethylene. 1,2-Dicyanocyclobutane (acrylonitrile dimer) also formed in these reactions,



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but we cannot say whether its formation was catalyzed or thermal (this compound was also noted in the thermal cycloadditions).

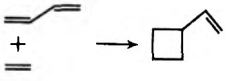
Discussion

Thermal Cycloaddition.—The cycloaddition of ethylene to acrylonitrile can be accomplished in modest yields. The conditions, involving 1000 atm of ethylene at 300–345°, cannot be described as convenient. Also, scrupulous precautions to avoid oxygen or adventitious initiators must be taken to avoid polymer and tar formation. Nevertheless, this cycloaddition does represent a synthesis of cyclobutanecarbonitrile from cheap starting materials.

The conversions are limited by equilibrium factors above 300°, as shown by the agreement for calculated equilibrium constants with those found and by the independence of yield with time. The thermodynamic equation for the section is very similar to that given by Back and coworkers[8] for cyclobutane, $\Delta F^\circ = -19{,}030 + 42.38T$. The cyano group, therefore, does not change the equilibrium position to any great extent.

This is not true, however, for the rates. Back and coworkers worked at 450–513° to obtain reasonable rates of cyclodimerization of ethylene. Our reaction proceeds at 300–345°, consistent with stabilization of the biradical intermediate by one cyano group. Stabilization by two cyano groups, in the cyclodimerization of acrylonitrile, permits a further lowering of reaction temperature to 200–240° with an accompanying greater equilibrium conversion to cyclodimer.[17]

Catalyzed Cycloaddition.—The possibility of metal-catalyzed cycloaddition of two olefins has been much discussed lately (for recent reviews, see ref 18). Experimental examples, however, have been limited until recently to strained olefins such as norbornene, norbornadiene, and 1-methylcyclopropene, and to conjugated dienes such as butadiene. Very recently, however, Cannell[19] showed that ethylene cycloadds to butadiene under the influence of tetrabenzyltitanium and related soluble titanium catalysts. Our discovery



of weak catalysis by nickel(0) compounds is the second example of the catalysis of an ethylene cycloaddition.

(17) Reports from several laboratories[5-7] agree that at 240–250° for 4 hr a 13–15% yield is obtained. At 200° a 5% yield is obtained in this time,[8] but this is undoubtedly kinetically controlled.

(18) For recent reviews, see (a) W. Keim in "Transition Metals in Homogeneous Catalysis," G. N. Schrauzer, Ed., Marcel Dekker, New York, N. Y., 1971, pp 59–91; (b) F. D. Mango and J. H. Schachtschneider, *ibid.*, pp 223–295.

(19) L. G. Cannell, *J. Amer. Chem. Soc.*, **94**, 6867 (1972).

TABLE V

"CATALYSIS" OF CYCLOBUTANECARBONITRILE FORMATION[a]

Tube volume, ml	Acrylonitrile, ml	Catalyst	Temp, °C	Time, hr	Cyclobutanecarbonitrile, mmol	1,2-Dicyanocyclobutane, mmol	Polymer
400	60	$(C_5H_5)_2Ni$	250	2	5	24	Moderate
400	60	$(C_5H_5)_2Ni$	250	4	8	28	Moderate
400	60	**3**	250	2	6–8	21–54	Moderate
400	30	$(C_5H_5)_2Ni$	275	2	7	5	Moderate

[a] Conditions: 1000 atm of ethylene, no solvent, 0.1 g of catalyst.

Experimental Section

Raman spectra were determined on a Cary Model 81 instrument equipped with a helium–neon laser. Thermodynamic properties were calculated using the formulas given by Colthup, *et al.*[16] The computer programs gave good agreement with test compounds from the literature.[20]

Pressure Tube Procedure (Table V).—A 400-ml, stainless steel shaker tube was flushed with nitrogen and the catalyst candidate or inhibitor was loaded under a stream of nitrogen. The tube was closed, cooled in Dry Ice–acetone and acetone, and alternately evacuated and flushed with nitrogen five times. A loading vessel charged with acrylonitrile and solvent was then connected to the evacuated tube and the acrylonitrile and solvent were transferred under vacuum. The tube was closed and filled with the desired amount of ethylene. After heating for the specified period of time, the tube was cooled in Dry Ice–acetone and the excess ethylene was vented very slowly through a gas trap cooled in Dry Ice–acetone. After the ethylene was vented, the contents were poured into a bottle and the tube was rinsed thoroughly with 20 ml of toluene. The rinse was placed in a separate bottle. The product mixture was flash distilled under reduced pressure into a gas trap cooled in liquid nitrogen until no further volatile material condensed. The polymer residue was analyzed for N. A small amount of tetramethylene sulfone was added to the distillate and rinse as an internal gc standard. The liquid samples were analyzed for acrylonitrile, cyclobutanecarbonitrile, 1,2-cyclobutanedicarbonitrile, and 2-methyleneglutaronitrile by gas chromatography. The gc column, used at 150° for the first two and 225° for the latter two, was a 6 ft × 0.25 in. stainless steel column packed with 20% silicone gum nitrile (XE-60) on 60/80 Chrom P; flow rate of 30 cc/min He.

The shaker tubes were conditioned by boiling them with dimethylformamide and drying under nitrogen.

Carius Tube Procedure (Table V).—The reaction vessel was a 60-ml heavy-walled glass Carius tube. The metal complex or catalyst candidate was placed in a drybox if the sample was air or moisture sensitive. The tube was connected with gum-rubber tubing to a glass three-way stopcock, which was connected to a vacuum pump and to a 2.25-l. stainless steel cylinder. The cylinder (which had been alternatively evacuated and filled with ethylene five times to remove oxygen) in turn was connected to a source of reagent grade ethylene. The Carius tube was evacuated to less than 0.1 mm pressure and then cooled in liquid N_2. The 2.25-l. cylinder was filled with the desired amount of ethylene (as indicated by a pressure gauge). The desired amount of acrylonitrile (Matheson Coleman and Bell Chromatoquality, purged with argon and dried over molecular sieves, Type 3A) was delivered into the tube with a hypodermic syringe through the rubber tubing connecting the tube to the stopcock (the tube leading to the pump was clamped off). The stopcock was then opened, allowing the ethylene to condense into the tube. Excess ethylene which had not condensed was pumped off. The tube was sealed and heated for 16 hr at 150–275° in a shielded oven. The tube was then cooled in liquid nitrogen and connected by means of a piece of gum-rubber tubing to a source of positive nitrogen. The glass tip of the tube was broken, and the excess ethylene was allowed to evaporate. The residual product was removed and analyzed by gc.

The column used was 21-in., 10% butanediol succinate on 60–80 Gas-Chrom Z. The column temperature was programmed for 100° (3 min) to 200° at 15°/min with a flow rate of 10 cc/6.5 in. Peak area ratios were translated into moles of acrylonitrile, and cyclobutanemono- or dicarbonitrile by the following formulas (TMS = tetramethylene sulfone, AN = acrylonitrile, CBN = cyclobutanecarbonitrile, DCN = 1,2-cyclobutanedicarbonitrile).

$$\text{mmol of AN} = \text{mmol of TMS}(2.0)\frac{\text{peak area AN}}{\text{peak area TMS}}$$

$$\text{mmol of CBN} = \text{mmol of TMS}(1.26)\frac{\text{peak area CBN}}{\text{peak area TMS}}$$

$$\text{mmol of DCN} = \text{mmol of TMS}(1.01)\frac{\text{peak area DCN}}{\text{peak area TMS}}$$

The conversion factors were determined by making up standard solutions with known amounts of AN and the cyclobutanecarbonitriles as well as TMS.

Calculations.—The results of Table I were converted to equilibrium constants as follows

$$K_{exp} = \frac{a_{CBN}}{a_{AN}a_E} = \frac{\gamma_{CBN}c_{CBN}}{\gamma_{AN}c_{AN}c_E}$$

where CBN = cyclobutanecarbonitrile, AN = acrylonitrile, E = ethylene, c's are concentrations, and a's are activities. The activity coefficients of the two nitriles are expected to be approximately equal and were cancelled. The activity coefficient of ethylene, γ_E, can be obtained by comparing the observed pressure to that calculated from the perfect gas law. Over the temperature ranges under consideration it had the value 1.66 ± 0.03. The values of c_E were obtained from the known gas densities, the pressure vessel volume, and the molecular weight of ethylene. Therefore

$$K_{exp} = \frac{\text{mmol CBN}_t}{(\text{mmol AN}_0 - \text{mmol CBN}_t)\cdot 1.66c_E}$$

The sources of error in this treatment include the loss of AN through dimerization and resin formation.

A brief attempt was made to calculate the equilibrium constant as the ratio of the rates of the forward and back reactions. The former were calculated for the runs at 225 and 250°. The latter were obtained by extrapolation of the reported thermolysis rates of cyclobutanecarbonitrile at much higher temperatures.[21] Agreement of the equilibrium constant obtained in this way with that calculated from thermodynamics was poor. However, the great difference in conditions under which the two rate constants were obtained ($k_{forward}$ at 225° in 1000 atm of supercritical ethylene; $k_{reverse}$ at 1 atm at 500°) is doubtless responsible.

Registry No.—Ethylene, 74-85-1; acrylonitrile, 107-13-1; cyclobutanecarbonitrile, 4426-11-3.

Acknowledgments.—We are deeply indebted to Miss Ellen Wallace for the laser Raman middle-infrared spectra; to Mrs. Ann Alexander of the Engineering Department for the computer programs for the thermodynamic properties; to the personnel of the Pressure Research Laboratory for endless pressure runs; to Drs. E. Bromels and S. C. Cherkofsky for helpful discussions; and to Professor R. C. Lord of the Massachusetts Institute of Technology, without whose invaluable assistance, patient encouragement, and contribution of data (together with Dr. C. S. Blackwell) this work could not have been performed.

(20) (a) Spiropentane: D. W. Scott, H. L. Finke, W. N. Hubbard, and J. P. McCullough, *J. Amer. Chem. Soc.*, **72**, 4668 (1950). (b) Chloroform: ref 16. (c) Ethylene: G. J. Janz, "Thermodynamic Properties of Organic Compounds," Academic Press, New York, N. Y., 1967, p 26. (d) Trifluoroacetonitrile: *ibid.*, p 22.

(21) S. Sarner, D. M. Gale, and A. B. Richmond, *J. Phys. Chem.*, **76**, 2817 (1972).

Notes

Thallium in Organic Synthesis. XXXVII. A New Synthesis of Arylnitroso Compounds[1]

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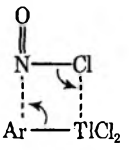
Previous papers in this series have demonstrated the effectiveness of thallium(III) trifluoroacetate (TTFA) as a thallating agent for aromatic compounds,[2,3] and have described procedures for the facile conversion of the resulting arylthallium ditrifluoroacetates into aryl iodides,[4,5] arylnitriles,[6] aryl isothiocyanates,[7] phenols,[6] thiophenols,[8] biaryls,[9] and deuterated aromatic compounds.[10] We now describe a simple method for the conversion of arylthallium ditrifluoroacetates into arylnitroso compounds by treatment with nitrosyl chloride (eq 1 and 2).[11]

$$ArTl(OOCCF_3)_2 + 2HCl \longrightarrow ArTlCl_2 + 2CF_3COOH \quad (1)$$

$$ArTlCl_2 + NOCl \longrightarrow ArNO + TlCl_3 \quad (2)$$

Thus, the organothallium intermediate is suspended in chloroform containing 1.5 equiv of *n*-propyl nitrite, and hydrochloric acid is added. The nitrosyl chloride generated *in situ* reacts with the arylthallium dichloride (formed from the arylthallium ditrifluoroacetate and HCl) to give the arylnitroso compound. Yields are moderate to good (Table I). Since the arylthallium ditrifluoroacetates can be recrystallized to isomeric purity, this reaction constitutes a novel and general method for the direct introduction of nitrogen functionalities into aromatic nuclei, with all of the orientation control potential inherent in the initial thallation process.[3,12]

Our previously described[6] synthesis of phenols from arylthallium ditrifluoroacetates, lead tetratrifluoroacetate, and trifluoroacetic acid in all probability involves (in the initial step of the overall conversion) electrophilic attack by lead(IV) on the aryl–thallium bond[13] to give an aryllead tris(trifluoroacetate), which then undergoes spontaneous decomposition to an aryl trifluoroacetate (which gives the phenol by hydrolysis). We suggest that the reaction of arylthallium ditrifluoroacetates with nitrosyl chloride is another example of electrophilic displacement of Tl(III) from the aromatic nucleus [the formation of Tl(III) rather than Tl(I) in this reaction was confirmed experimentally], and that it may proceed through a four-centered transition state arising from initial complexation of nitrosyl chloride with the organothallium substrate.[14] Indeed, electrophilic substitution on the carbon–thallium bond of $ArTlX_2$ compounds may be a general process[15] provided only that initial complexation of the $ArTlX_2$ substrate precedes or accompanies attack by the electrophile. We are currently exploring this potentially new and versatile method for the introduction of electrophiles into aromatic systems.



Experimental Section

General Procedure for the Conversion of Arylthallium Ditrifluoroacetates to Arylnitroso Compounds.—*n*-Propyl nitrite (0.015 mol) was added to a suspension of the arylthallium ditrifluoroacetate (0.01 mol) in 100 ml of chloroform at room temperature. A solution of 12 *N* hydrochloric acid (4 ml) and glacial acetic acid (6 ml) was added with vigorous stirring.[18] The white precipitate which immediately formed (arylthallium dichloride) dissolved within minutes to give a green solution. After 10 min of stirring, 50 ml of 1.2 *N* hydrochloric acid was added, the mixture was stirred for 10 min, and the green chloroform layer was separated and extracted with 0.1 *N* hydrochloric acid (to remove

(1) Part XXXVI: E. C. Taylor, R. L. Robey, and A. McKillop, *J. Org. Chem.*, **37**, 2797 (1972).

(2) A. McKillop, J. S. Fowler, M. J. Zelesko, J. D. Hunt, E. C. Taylor, and G. McGillivray, *Tetrahedron Lett.*, 2423 (1969).

(3) E. C. Taylor, F. Kienzle, R. L. Robey, A. McKillop, and J. D. Hunt, *J. Amer. Chem. Soc.*, **93**, 4845 (1971).

(4) A. McKillop, J. S. Fowler, M. J. Zelesko, J. D. Hunt, E. C. Taylor, and G. McGillivray, *Tetrahedron Lett.*, 2427 (1969).

(5) A. McKillop, J. S. Fowler, M. J. Zelesko, J. D. Hunt, E. C. Taylor, F. Kienzle, and G. McGillivray, *J. Amer. Chem. Soc.*, **93**, 4841 (1971).

(6) E. C. Taylor, H. W. Altland, R. H. Danforth, G. McGillivray, and A. McKillop, *ibid.*, **92**, 3250 (1970).

(7) E. C. Taylor, F. Kienzle, and A. McKillop, *Synthesis*, 38 (1972).

(8) E. C. Taylor and A. McKillop, *Accounts Chem. Res.*, **3**, 338 (1970).

(9) E. C. Taylor, F. Kienzle, and A. McKillop, *J. Amer. Chem. Soc.*, **92**, 6088 (1970).

(10) M. J. Zelesko, Ph.D. Thesis, Princeton University, 1970.

(11) Arylmercury [L. I. Smith and F. L. Taylor, *J. Amer. Chem. Soc.* **57**, 2460 (1935)], -magnesium [B. Oddo, *Gazz. Chim. Ital.*, **39**, I, 659 (1909)], and -tin [E. H. Bartlett, C. Eaborn, and D. R. M. Walton, *J. Chem. Soc. C*, 1717 (1970)] compounds react analogously with nitrosyl chloride.

(12) E. C. Taylor, F. Kienzle, R. L Robey, and A. McKillop, *J. Amer. Chem. Soc.*, **92**, 2175 (1970).

(13) Trans metalation reactions of this type have been viewed as an electrophilic substitution reaction on the original aryl–metal bond: R. Criegee, P. Dimroth, and R. Schempf, *Chem. Ber.*, **90**, 1337 (1957).

(14) Thallium is known to be capable of expansion of its coordination sphere; complexes with halide and cyanide ions are well known.[15]

(15) A. G. Lee, "The Chemistry of Thallium," Elsevier, Amsterdam, 1971.

(16) Protodethallation[15,17] is still a further example of an electrophilic "displacement" of Tl(III) from the aromatic ring.

(17) A. N. Nesmeyanov and K. A. Kocheshkov, "Methods of Elemento-Organic Chemistry. Vol. 4. The Organic Compounds of Boron, Aluminium, Gallium, Indium, and Thallium," North-Holland Publishing Co., Amsterdam, 1967.

(18) 12 *N* hydrochloric acid alone was used with arylthallium ditrifluoroacetates derived from less reactive aromatic substrates (*i.e.*, chlorobenzene).

TABLE I

SYNTHESIS OF ARYLNITROSO COMPOUNDS FROM ARYLTHALLIUM DITRIFLUOROACETATES

$ArTl(OOCCF_3)_2 \longrightarrow ArNO$

Registry no.	Product[a]	Registry no.[l]	Yield, %
1516-21-8	4-Nitrosoanisole	28688-23-5	59[b]
586-96-9	Nitrosobenzene	23586-54-1	43[c]
932-98-9	4-Nitrosochlorobenzene	23586-58-5	50[d]
38899-21-7	Nitrosodurene	38899-26-2	93[e]
1196-12-9	Nitrosomesitylene	23586-57-4	93[f]
22955-65-3	4-Nitrosoethylbenzene	35322-30-6	88[g]
623-11-0	4-Nitrosotoluene	23586-55-2	88[h]
38899-22-8	4-Nitroso-1,2-dimethylbenzene	23586-56-3	91[i]
38974-06-0	4-Nitroso-1,3-dimethylbenzene	34202-98-7	90[j]
17075-25-1	2-Nitroso-1,4-dimethylbenzene	34202-99-8	93[k]

[a] The use of isomerically pure arylthallium ditrifluoroacetates led to the formation of isomerically pure arylnitroso compounds; otherwise, mixtures of isomeric arylnitroso compounds were obtained whose isomeric distribution matched that of the starting material (see Experimental Section). [b] A. Baeyer and E. Knorr, *Ber.*, **35**, 3034 (1902); mp 32–34°. [c] "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 668; mp 64–67°. [d] R. E. Lutz and M. R. Lytton, *J. Org. Chem.*, **2**, 68 (1937); mp 89.5°. [e] L. I. Smith and F. L. Taylor, *J. Amer. Chem. Soc.*, **57**, 2460 (1935); mp 160° dec. [f] E. Bamberger and A. Rising, *Ber.*, **33**, 3623 (1900); mp 122°. [g] See footnote *d*; mp 22°. [h] E. Bamberger, *Ber.*, **28**, 245 (1895); mp 48.5°. [i] E. Bamberger and A. Rising, *Justus Liebigs Ann. Chem.*, **316**, 257 (1901); mp 44–45°. [j] See footnote *i*; mp 41.5°. [k] See footnote *i*; mp 101.5°. [l] Of starting material.

$TlCl_3$). The chloroform extract was dried ($MgSO_4$) and evaporated to give the crude arylnitroso compound, which was purified by Kugelrohr distillation (*in vacuo*).

Glc analysis of the arylnitroso compounds was frustrated by poor separation and, as a consequence, isomer distributions were determined by oxidation with pertrifluoroacetic acid to the arylnitro compounds, which were then satisfactorily analyzed by glc. As expected, the use as substrates of arylthallium ditrifluoroacetates which had not been recrystallized to isomeric purity led to a mixture of isomeric arylnitroso compounds whose isomeric distribution matched precisely that of the precursor arylthallium ditrifluoroacetates. Thus in this reaction, as in all previously investigated conversions of $ArTlX_2$ compounds to substituted aromatics, the new substituent group enters the ring at the position to which the thallium atom was originally attached.

Kinetic Evidence for an Enamine Mechanism in the Acid-Catalyzed Cleavage of β-Amino Alcohols[1]

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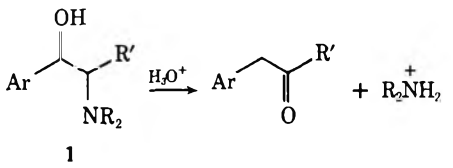
The reaction of α-aryl-β-amino alcohols with strong acids has been known for some time to cause cleavage to β-carbonyl compounds.[2-4] Two mechanisms have been proposed to account for the cleavage, one involving a glycol intermediate[2,3] and the other involving



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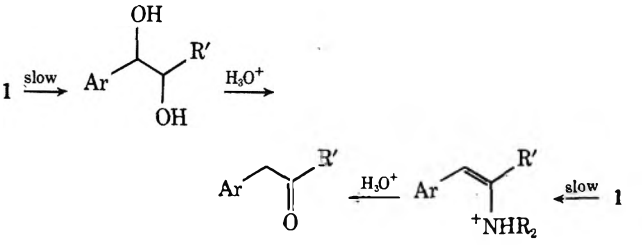

an enamine intermediate.[2,4] The details of these mechanisms have been reviewed recently.[5] In general there has been little convincing experimental evidence in favor of either mechanism, although recent work[5] has ruled out a glycol mechanism for the reaction of one amino alcohol with acid.

We have examined the acid-catalyzed reaction rates of 2-(*N*,*N*-diethylamino)-1-phenylethanol derivatives having from zero to three methyl groups on the aromatic rings. A large excess of 4 *N* hydrochloric acid at 100° was employed as the reaction medium, conditions which led to pseudo-first-order kinetics. Ultraviolet spectroscopy was used to monitor the disappearance of amino alcohols. The pseudo-first-order rate constants and relative rates are summarized in Table I.

TABLE I

GRAPHICALLY DETERMINED PSEUDO-FIRST-ORDER RATE CONSTANTS AND RELATIVE RATES FOR REACTION OF AMINO ALCOHOLS WITH 4 *N* HYDROCHLORIC ACID AT 100°

Registry no.	Amino alcohol	k, sec^{-1}	Relative rate
4249-64-3	$C_6H_5CHOHCH_2NEt_2$	2.63×10^{-7}	1.00
39008-11-2	p-$CH_3C_6H_4CHOHCH_2NEt_2$	2.19×10^{-6}	8.33
39008-12-3	2,4-di-$CH_3C_6H_3CHOHCH_2NEt_2$	1.61×10^{-5}	61.2
39008-13-4	2,4,6-tri-$CH_3C_6H_2CHOHCH_2NEt_2$	8.14×10^{-5}	309

The rate constants are seen to increase with increasing methyl substitution on the ring, each increase by one methyl group leading to an increase in rate by a factor varying from approximately 5 to 8. A mech-

(1) The receipt of an NSF and a Lafayette summer fellowship and a grant from Merck Sharpe and Dohme, Inc., in support of this research is gratefully acknowledged.

(2) F. Kröhnke and A. Schulze, *Chem. Ber.*, **75**, 1154 (1942).

(3) H. Auterhoff and H. J. Roth, *Arch. Pharm. (Weinheim)*, **289**, 470 (1956).

(4) P. T. Sou, *Bull. Fac. Sci. Univ. Fr-Chin. Peiping*, **5**, 1 (1935); *Chem. Abstr.*, **30**, 4463 (1936).

(5) S. A. Fine and R. L. Stern, *J. Org. Chem.*, **35**, 1857 (1970).

anism involving glycol intermediacy has a rate-determining step involving nucleophilic attack at the carbon atom bearing the diethylamino group,[5] whereas an enamine mechanism involves a rate-determining dehydration with consequent carbonium ion formation. The rate data are consistent with the latter process and follow a trend noted by previous workers in the solvolysis of 1-phenylethyl chlorides. Thus, at 0°, the relative rates of ethanolysis of 1-phenylethyl chloride, 1-*o*-tolylethyl chloride, and 1-mesitylethyl chloride were approximately 1:34:3500,[6] while at 25° the ratio was 1:22:1980.[6] Although the *p*-methyl compound was not included in the solvolysis study, the rate-enhancing effect of a *p*-methyl group on typical solvolysis reactions of benzylic compounds varies from fourfold to 80-fold, depending on the specific compound and reaction conditions.[7] In the case of *o*-methyl groups two competing effects operate: an inductive effect which stabilizes the carbonium ion, and a steric effect which destabilizes the ion by hindering coplanarity of the ion with the aromatic ring. It has been suggested that ions of the type $o\text{-}CH_3C_6H_4CHR^+$ suffer no significant steric inhibition of resonance but when two *o*-methyl groups are present inhibition does occur, but is surpassed by stabilizing inductive effects.[6] Our rate data also shows a greatly enhanced rate of reaction for the mesityl compound, but the increase in reactivity of the mesityl compound compared to the 2,4-dimethyl compound is smaller than the increase in reactivity of the 2,4-dimethyl compound compared to the *p*-methyl compound and of the *p*-methyl compound compared to the unsubstituted amino alcohol.

Additional evidence is provided by a comparison of our rate data with rate data for the acid-catalyzed dehydrations of other 1-phenylethanol derivatives. Thus, ρ for the reaction of the amino alcohols is approximately -3.1 (σ^+ para) compared with typical values in the -3 to -4 range for reactions of the latter type.[8,9]

In contrast, a bimolecular rate-determining step is not consistent with the present results.[10] Even for compounds in which the group being displaced is on a benzylic carbon, there is always less than a twofold difference in the rates of *p*-tolyl *vs.* phenyl in typical SN2 reactions.[11]

Experimental Section[12]

Synthesis of Amino Alcohols.—2-(*N*,*N*-Dimethylamino)-1-phenylethanol was prepared by a previously published procedure.[13] All other amino alcohols were prepared *via* the following general procedure. A solution of Br_2 (32 g, 0.20 mol) in CCl_4 (125 ml) was added at a slow dropwise rate[14] to a vigorously stirred solution of the appropriate ketone (0.20 mol) in CCl_4 (175 ml). The solution was stirred for 20 min and approximately 75% of the solvent was evaporated under reduced pressure. The concentrated solution was cooled to 0° and the bromo ketone was collected, washed with cold hexane, and air dried.

The bromo ketone (10 g) was added in small portions to a large excess (35 ml) of vigorously stirred diethylamine at 0°. After stirring for 2 hr at 0° the reaction mixture was kept under N_2 at 30° for 24 hr. Excess Et_2NH was removed under reduced pressure and the residue was extracted with ether and filtered from $Et_2NH \cdot HBr$. The ether layer was extracted with two 50-ml portions of cold 2 *N* HCl and the aqueous extract was then neutralized (NaOH). The crude product was reextracted with ether, solvent was removed under reduced pressure, and the amino ketone was vacuum distilled.

A solution of the amino ketone (0.03 mol) in anhydrous ether was added dropwise to a stirred mixture of $LiAlH_4$ (0.013 mol) in anhydrous ether. After addition was complete the mixture was refluxed for 30 min. Water-saturated ether was added cautiously to destroy excess $LiAlH_4$. The ether layer was separated and washed with water, sodium carbonate, and water. Drying of the ether solution ($MgSO_4$) followed by evaporation of solvent under reduced pressure gave the amino alcohol, which was purified by vacuum distillation. Overall yields of the amino alcohols were generally 30–40%. The results of these preparations are summarized in Table II.

TABLE II

SUMMARY OF PHYSICAL AND SPECTRAL PROPERTIES OF AMINO ALCOHOLS[a] SYNTHESIZED BY THE PROCEDURE BELOW

$$ArCOCH_3 \xrightarrow{Br_2} ArCOCH_2Br \xrightarrow{Et_2NH} ArCOCH_2NEt_2 \xrightarrow{LiAlH_4} ArCHOHCH_2NEt$$

Compd	Bp, °C (mm)	Ir,[b] cm^{-1}	Uv,[c] nm
$C_6H_5CHOHCH_2NEt_2$			λ_{max} 256 (ϵ 192)
$p\text{-}CH_3C_6H_4CHOHCH_2NEt_2$	135 (5)[d]	3380 (m, OH)	λ_{max} 261.5 (ϵ 331)
2,4-di-$CH_3C_6H_3CHOHCH_2NEt_2$	145 (5)	3410 (m, OH)	λ_{max} 264.5 (ϵ 334)
2,4,6-tri-$CH_3C_6H_2CHOHCH_2NEt_2$	153 (5)[e]	3390 (m, OH)	λ_{max} 267 (ϵ 330)

[a] Satisfactory elementary microanalyses were obtained for all new amino alcohols. [b] Spectra were determined on neat liquids; no absorption in the C=O region was present in any of the amino alcohol spectra. [c] Ultaviolet spectra were determined as dilute HCl solutions. [d] Lit.[10] bp 102–104° (0.2 mm). [e] Solidified on standing, mp 57–58°.

Determination of Reaction Rates of Amino Alcohols with 4 *N* Hydrochloric Acid. General Procedure.—A tightly stoppered 50-ml flask containing 35 ml of 4 *N* HCl and a Teflon-coated stirring bar was placed in a magnetically stirred oil bath maintained at 100° by means of an electronic temperature controller.[15] After 1 hr the amino alcohol (300–500 mg) was introduced into the flask and timing was begun. At various times 1-ml aliquots were pipetted from the reaction mixture into a 25-ml volumetric flask containing 20 ml of cold water. The solution was washed four times with ether,[16] the ether being removed each time by careful suction with a disposable pipette. The aqueous solution was diluted to 25 ml with water and the ultraviolet absorbance of the solution at λ_{max} was determined. The solutions obtained after 1-min reaction times were used for zero-point readings, the rate constants being such that the extents of reaction were usually negligible after 1 min. The reference blank consisted of a sample of 4 *N* HCl, carried through the same procedure as the

(6) G. Baddeley and J. Chadwick, *J. Chem. Soc.*, 368 (1951).

(7) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N.Y., 1962, p 76.

(8) N. C. Deno, F. A. Kish, and H. J. Peterson, *J. Amer. Chem. Soc.*, **87**, 2157 (1965).

(9) D. S. Noyce, D. R. Hartler, and F. B. Miles, *J. Amer. Chem. Soc.*, **90**, 3794 (1968).

(10) The reaction of $PhCHOHCH_2OH$ with 1.78 *M* sulfuric acid is at least 70% complete in 1 hr: T. Matsuda and M. Sugishita, *Bull. Chem. Soc. Jap.*, **35**, 1446 (1962). Under our (similar) conditions $PhCHOHCH_2NEt_2$ required several days for half-reaction; hence, although diols dehydrate *via* a carbonium ion mechanism, the reaction of the diols to form carbonium ions could not be rate determining for the amino alcohols in this investigation if a diol mechanism were involved.

(11) Reference 7, p 18.

(12) Ketone starting materials were obtained commercially and were distilled before use. Melting points were taken on a Fisher-Johns block and are uncorrected. Infrared spectra were recorded on a Beckman IR-10 instrument. Ultraviolet spectra were recorded on a Beckman DK-2A spectrophotometer; reactions were monitored on a Beckman DU instrument. Elemental microanalyses were performed by Dr. George I. Robertson, Jr., Florham Park, N.J.

(13) S. L. Shapiro, H. Soloway, and L. Freedman, *J. Amer. Chem. Soc.*, **80**, 6060 (1958).

(14) Addition was stopped as soon as a Br_2 color persisted.

(15) Cole-Parmer Versatherm Model 2156 proportional electronic temperature controller.

(16) The ether washes served to remove the aldehyde products, which might otherwise interfere with the uv measurements.

samples. The results of the experiments and a representative run are tabulated in Tables I and III.

TABLE III
REPRESENTATIVE RUN.
RAW KINETIC DATA FROM THE REACTION OF 2-(*N*,*N*-DIETHYLAMINO)-1-(2,4,6-TRIMETHYLPHENYL)ETHANOL WITH 4 *N* HCl AT 100°

Time, min	Absorbance (at 267 nm)
0	0.547
19	0.432
37	0.346
58	0.282
79	0.225
98	0.184
118	0.152

Registry No.—$ArCOCH_3$ (Ar = C_6H_5), 98-86-2; $ArCOCH_3$ (Ar = *p*-$CH_3C_6H_4$), 122-00-9; $ArCOCH_3$ (Ar = 2,4-di-$CH_3C_6H_3$), 89-74-7; $ArCOCH_3$ (Ar = 2,4,6-tri-$CH_3C_6H_2$), 1667-01-2; $ArCOCH_2Br$ (Ar = C_6H_5), 70-11-1; $ArCOCH_2Br$ (Ar = *p*-$CH_3C_6H_4$), 619-41-0; $ArCOCH_2Br$ (Ar = 2,4-di-$CH_3C_6H_3$), 26346-85-0; $ArCOCH_2Br$ (Ar = 2,4,6-tri-$CH_3C_6H_2$), 4225-92-7; $ArCOCH_2NEt_2$ (Ar = C_6H_5), 4061-29-4; $ArCOCH_2NEt_2$ (Ar = *p*-$CH_3C_6H_4$), 39008-15-6; $ArCOCH_2NEt_2$ (Ar = 2,4-di-$CH_3C_6H_3$), 39008-16-7; $ArCOCH_2NEt_2$ (Ar = 2,4,6-tri-$CH_3C_6H_2$), 39008-17-8; Br_2, 7726-95-6; $LiAlH_4$, 16853-85-3; diethylamine, 109-89-7.

An Improved Synthesis of 2-Chloro-2-fluoropropane

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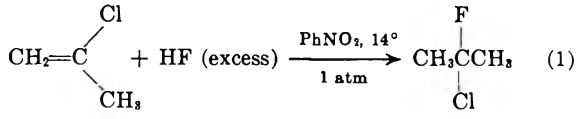
2-Chloro-2-fluoropropane (**1**) was first prepared in 10–15% yield by the action of antimony trifluoride containing 5% bromine on 2,2-dichloropropane in 1937 by Henne.[1] Small yields of **1** can also be prepared[2] by heating $(CH_3)_2CClN(O)=NF$ to 60° and by the action of chlorine in the liquid or gas phase on 2-fluoropropene.[3-5] The free-radical chlorination of 2-fluoropropane gave 2-chloro-2-fluoropropane in 77% yield.[6] Henne[7] found that the reaction of 2-chloropropene with anhydrous fluoride (without solvent) yielded a mixture of 2,2-difluoropropane and 2,2-dichloropropane instead of the simple addition product **1**. However, Chapman[8] did obtain a 47% yield of **1** by the stannic chloride catalyzed addition of anhydrous hydrogen fluoride to 2-chloropropene.

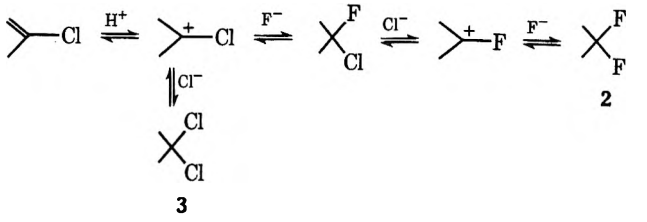
We have found that the simple addition of hydrogen fluoride to 2-chloropropene to produce **1** can be achieved very smoothly and in high yield (75%) when the reaction is carried out in nitrobenzene at 14° for 10 min, as shown in eq 1. The use of nitrobenzene moderated



(1)

the reactivity of hydrogen fluoride and permitted the clean addition of HF across the double bond without further reaction to produce 2,2-difluoropropane (Scheme I) or the formation of tars. Reaction times greater

SCHEME I



than 10 min led to a disproportionation, producing 2,2-difluoropropane (**2**) and 2,2-dichloropropane (**3**) as shown in Scheme I. The disproportionation products **2** and **3** were readily distinguished from **1** by their nmr spectrum. The methyl absorption of **2** was a triplet, of **3** was a singlet, and of **1** was a doublet.

The yield (75%) was based on isolated material. However, an nmr spectrum of the crude reaction mixture showed no products other than **1** and indicates, if allowances are made for recovered starting material and for evaporation (bp 35°) of product during work-up, that the addition is highly efficient.

Experimental Section

To 80 ml of nitrobenzene (dried, reagent) in a 125-ml Teflon bottle containing a Teflon-coated magnetic stirring bar was added 10.0 g (0.130 mol) of 2-chloropropene. Anhydrous hydrogen fluoride gas was rapidly added to the cooled (14°) mixture until 22 g (1.1 mol) had been absorbed. The mixture was allowed to stir for 10 min, and then rapidly added to cold water. Carbon tetrachloride (300 ml) was added, the organic layer was washed three times with water and dried (Na_2SO_4), and the solution was distilled on a spinning band column to yield 10.7 g of liquid, bp < 50° (mostly 35°). Integration of the pmr spectrum indicated that 13 mol % (11 wt %) of the isolated material was 2-chloropropene. Thus a yield of 75% and an efficiency of 89% were realized. The sample was redistilled on a spinning band column to obtain pure 2-chloro-2-fluoropropane: bp 33–35°; ir 824 and 604 cm^{-1}; pmr ($CDCl_3$) (60 MHz) δ 1.99 (d, J = 19.0 Hz); pmr (acetone-d_6) (100 MHz) δ 1.85 (d, J = 19.0 Hz); ^{19}F nmr (acetone-d_6) (100 MHz) δ 10.42 upfield from external CF_3CO_2H (septet, J = 19.0 Hz); mass spectrum (70 eV) m/e (rel intensity) 96 (0), 83 (7), 81 (20), 61 (100), 59 (11), 45 (13), 41 (36), 39 (15), 33 (7), 27 (6).

Registry No.—**1**, 420-44-0; 2-chloropropene, 557-98-2; hydrogen fluoride, 7664-39-3.

(1) A. L. Henne and M. W. Renoll, *J. Amer. Chem. Soc.*, **59**, 2424 (1937).
(2) A. N. Medvedev, K. N. Smirnov, S. S. Dubov, and V. A. Ginsburg, *Zh. Obshch. Khim.*, **38**, 2462 1968); *Chem. Abstr.*, **70**, 46737u (1969).
(3) J. P. Henry and L. O. Moore, U. S. Patent 3,215,746 (1965); *Chem. Abstr.*, **64**, P6492e (1966).
(4) J. P. Henry and L. O. Moore, U. S. Patent 3,277,188 (1966); *Chem. Abstr.*, **66**, P10571x (1967).
(5) L. D. Moore, J. P. Henry, and J. W. Clark, *J. Org. Chem.*, **35**, 4201 (1970).
(6) L. G. Anello and C. Woolf, Belgian Patent 632,995 (1963); *Chem. Abstr.*, **60**, P15730b (1964).
(7) A. L. Henne and P. Plueddeman, *J. Amer. Chem. Soc.*, **65**, 1271 (1943).
(8) J. Chapman and R. Roberts, U. S. Patent 2,495,407 (1950); *Chem. Abstr.*, **44**, P4020c (1950).

The Synthesis of 1-Pentyne-3,4-dione 4-Ethylene Ketal

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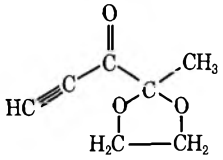
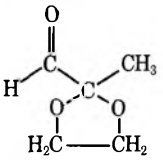
In the course of studies relating to the synthesis of a natural product, title compound **1** was required. Since a flexible synthesis was preferred (to allow for the facile interchange of the ethynyl unit for a vinyl grouping), the first goal was the synthesis of methylglyoxal 2-ethylene ketal (**2**).



1

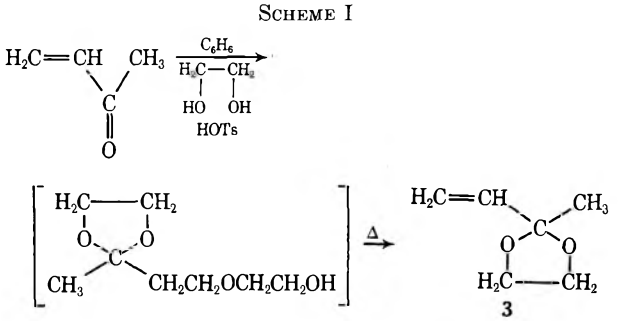


2

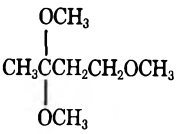
Although a number of synthetic schemes could be employed, considerations of practicality in operation on a large scale and availability of reagents limited the choice. The double bond in methyl vinyl ketone (MVK) may be viewed as masking a carbonyl group, the latter being generated by oxidative cleavage of the double bond. Thus, it was felt that, if the carbonyl function of MVK could be ketalized without disturbing the double bond, *i.e.*, polymerization, compound **2** would be readily in hand.

MVK reacted with ethylene glycol (*p*-toluenesulfonic acid as catalyst) and yielded a crude product whose infrared spectrum contained no absorption in the carbonyl region. Careful distillation of this material afforded a product which was identified as **3**. Although the intermediate was not characterized, based on the nmr spectrum which showed the absence of vinyl protons, and new absorptions in the area of δ 1.7–2.0, it is assumed that an initial addition of ethylene glycol to MVK occurs. Subsequently, ketalization of the carbonyl function takes place, and yields the crude product that was isolated. This ether, apparently unstable to heat, eliminates ethylene glycol to give **3** (Scheme I).

SCHEME I



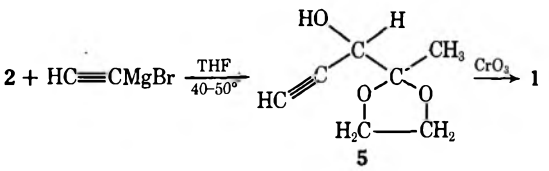
The above results are in accord with those reported by Dolby and Marshall,[2] who treated MVK with triethyl orthoformate to obtain **4**.



4

The aldehyde function was then readily generated by ozonolysis of **3** and reduction of the ozonide with triethyl phosphite.[3] Compound **2**, a clear liquid, was obtained after distillation. Ketal **2** reacted with ethynylmagnesium bromide[4] to give **5**, which was carefully oxidized by titrating a stirred solution of the ethynyl alcohol in acetone at 15–20° with Jones reagent[5] to give **1** (Scheme II).

SCHEME II



5

Experimental Section

The ir spectra were recorded on a Beckman IR-8 instrument. The mass spectral data was obtained on an MS-9 instrument. The nmr data was gathered from a Varian A-60A instrument. All chemical shifts reported are in parts per million (δ) with tetramethylsilane serving as the internal standard. Coupling constants (J) are quoted in hertz. Gas chromatography was done using an Aerograph A90-P3 instrument. The column used was SE-30 (5%) on Chromosorb P (13 ft × 0.375 in.), column temperature was 185°, and the flow rate (helium gas) was 75 ml/min. Boiling points are uncorrected. All solvents are of AR purity except in experiments where a method of purification is specified. Unless otherwise stated, drying involves the use of anhydrous sodium sulfate. All solvents were evaporated using a Büchi Rotovapor.

1-Buten-3-one Ethylene Ketal (3).—MVK (17.5 g, 0.5 mol), ethylene glycol (51 ml, 0.9 mol), and *p*-toluenesulfonic acid (200 mg, 0.001 mol) were heated under reflux in 500 ml of benzene for 4 hr while water was collected in a water separator. Glc showed that no starting ketone was left. The reaction was cooled, and the benzene was evaporated under vacuum. The remaining liquid was carefully distilled under high vacuum to yield approximately 22.5 g of product boiling at 28–31° (5 Torr) [104–107° (760 Torr)], indicating an essentially quantitative reaction. Spectral data was obtained on a sample that was pure by glc analysis: nmr ($CDCl_3$) δ 1.47 (s, 3 H), 3.92 (s, 2 H), 3.94 (s, 2 H), 5.1–5.9 (m, 3 H); ir (neat) λ_{max} 3.35, 3.45, 7.30, 8.3 (broad), 9.6 (broad), 11.6 μ. The clear liquid began to darken when left at room temperature for a number of days.

Methylglyoxal 2-Ethylene Ketal (2).—Compound **3** (18.5 g, 0.16 mol) was dissolved in 200 ml of dry methanol. The flask was fitted with a gas inlet and outlet tube, and was cooled to −70°. Ozone, generated *via* a Welsbach ozonator, was bubbled through for about 3 hr, until a 10% potassium iodide solution was darkened. Oxygen was passed through the reaction for 15 min to remove dissolved ozone. Triethyl phosphite (36 ml) was carefully added over a period of 1 hr. The reaction was kept at −70° for an additional 30 min, and then was allowed to warm to room temperature. The methanol was evaporated under vacuum, and the remaining liquid was carefully distilled at reduced pressure to yield approximately 17 ml of product boiling at 32–35° (5 Torr). Spectral data were obtained on a sample pure by glc analysis: nmr ($CDCl_3$) δ 1.43 (s, 3 H), 4.04 (s, 4 H), 9.4 (s, 1 H); ir (neat) λ_{max} 3.55, 5.78, 8.4 (broad), 9.6 μ (broad); mass spectrum parent ion − 15 (loss of CH_3), parent ion − 29

(1) NIH Predoctoral Fellow, 1967–1970. Address correspondence to Institute for Steroid Research, Montefiore Hospital and Medical Center, 111 E. 210th St., Bronx, New York 10467.

(2) L. J. Dolby and K. S. Marshall, *Org. Prep. Proced.*, **1**, 229 (1969).

(3) W. S. Knowles and Q. E. Thompson, *J. Org. Chem.*, **25**, 1031 (1960).

(4) L. Skattebol, E. R. H. Jones, and M. C. Whiting, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 792.

(5) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(loss of CHO). The clear liquid began to darken when left at room temperature for a number of days.

1-Pentyne-3-hydroxy-4-one Ethylene Ketal (5).—Compound **2** (5 g, 43 mmol) was dissolved in tetrahydrofuran distilled from calcium hydride (20 ml) and added to a solution of ethynylmagnesium bromide, prepared from magnesium (2 g, 83 g-atoms), ethyl bromide (6 ml, 84 mmol), and acetylene gas, over a 30-min period. The reaction was stirred at room temprature under a positive pressure of nitrogen for an additional 12 hr. The brown reaction mixture was then carefully poured onto a cooled solution of saturated ammonium chloride. The aqueous phase was extracted with three 150-ml portions of ether. The combined ether extracts were dried, filtered, and evaporated under vacuum. Glc of the yellow oil obtained indicated that one product had formed in essentially quantitative yield. The oil could be distilled under high vacuum to yield a clear liquid boiling at 112–118° (5 Torr). In actual practice the product obtained was pure enough to carry through to the next reaction. The product was stored in the cold, since it readily darkened at room temperature. Spectra data were obtained on a sample that was pure by glc analysis: nmr (CCl_4) δ 1.32 (s, 3 H), 2.29 (d, J = 2 Hz, 1 H), 2.87 (s, 1 H), 3.92 (s, 2 H), 3.94 (s, 2 H), 4.09 (d, J = 2 Hz, 1 H); ir (neat) λ_{max} 2.8 (broad), 3.05, 4.72, 9.4 (broad), 9.6 μ; mass spectrum m/e 142 (parent ion).

1-Pentyne-3,4-dione 4-Ethylene Ketal (1).—Compound **5** (20 g, 0.14 mol) was dissolved in acetone (100 ml) in a three-neck flask fitted with an overhead stirrer and a 125-ml addition funnel. The reaction was cooled to 0° and stirred vigorously. The Jones reagent was added dropwise over a period of 1 hr until a red color persisted (65 ml). The reaction was filtered and the green chromium salts were washed with ether. The aqueous phase was extracted with three 150-ml portions of ether. The ether extracts were combined and back-washed once with saturated sodium chloride solution. The ether extracts were then dried, filtered, and evaporated under vacuum. Glc of the yellow liquid obtained indicated that only one product had formed, with the yield being greater than 90%. The yellow liquid could be distilled under high vacuum to yield a colorless liquid boiling at 65–71° (5 Torr), which darkened if kept out of the freezer for a prolonged period of time. Spectral data was obtained on a sample pure by glc analysis: nmr (CCl_4) δ 1.40 (s, 3 H), 3.31 (s, 1 H), 3.97 (s, 4 H); ir (neat) λ_{max} 3.08, 4.79, 5.92 8.3 (broad), 9.8 μ (broad); mass spectrum parent ion − 15 (loss of CH_3), parent ion − 53 (loss of C_3HO).

Registry No.—**1**, 39050-38-9; **2**, 39050-39-0; **3**, 26924-35-6; **5**, 39050-41-4; MVK, 78-94-4; ethylene glycol, 107-21-1.

Acknowledgments.—The author would like to thank Professor H. Muxfeldt for helpful discussions. This research was supported by the National Institutes of Health (Grant GM 37701).

Synthesis of 2-Substituted 2,4a-Ethanophenanthrenes

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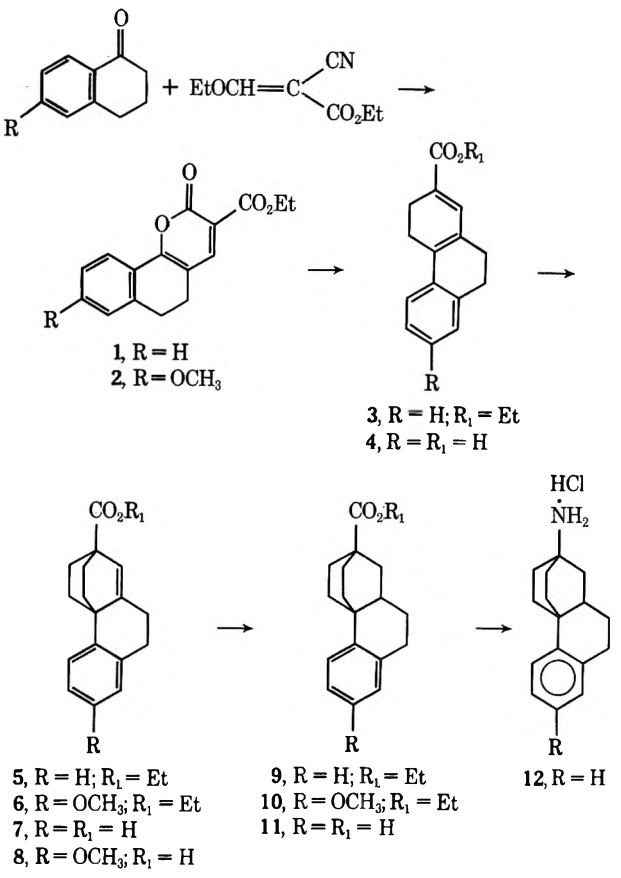
The 2,4a-ethanophenanthrene ring system has been little explored in the chemical literature.[1]

This paper describes a novel two-step synthetic route to the 2,4a-ethanophenanthrene ring system (Scheme I).

(1) N. P. Shusherina, R. Ya. Levina, and L. V. Kondrat'eva, *Zh. Obshch. Khim.*, **27**, 2255 (1957); N. P. Shusherina, N. O. Dmitrieva, and R. Ya. Levina, *ibid.*, **32**, 213 (1962); N. N. Girotra and L. H. Zalkow, *Tetrahedron*, **21**, 101 (1965).

SCHEME I



Base-condensation of α-tetralone with ethyl ethoxymethylenecyanoacetate followed by hydrolysis afforded ethyl 5,6-dihydro-2-oxo-2*H*-naphtho[1,2-*b*]pyran-3-carboxylate (**1**). The pyran **1** was allowed to react with ethylene at 3000 atm to give ethyl 2,3,4,4a,9,10-hexahydro-2,4a-ethanophenanthrene-2-carboxylate (**5**). The use of ethylene at 1000 atm gave the intermediate ethyl 3,4,9,10-tetrahydrophenanthrene-2-carboxylate (**3**).

Hydrogenation of **5** yielded ethyl 1,2,3,4,4a,-9,10,10a-octahydro-2,4a-ethanophenanthrene-2-carboxylate (**9**). The structure of esters **3**, **5**, and **9** were characterized by conversion to the corresponding carboxylic acids **4**, **7**, and **11**.

Similarly, ethyl 7-methoxy-1,2,3,4,4a,9,10,10a-octahydro-2,4a-ethanophenanthrene-2-carboxylate (**10**) was prepared from 6-methoxy-α-tetralone.

1,2,3,4,4a,9,10,10a-Octahydro-2,4a-ethanophenanthrene-2-amine hydrochloride (**12**) was synthesized from the corresponding acid **11**.

Experimental Section

Melting points were determined on a Thomas-Hoover "Unimelting" apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 21 spectrometer in Nujol. Nmr spectra were obtained on a Varian A-60 spectrometer with $(CH_3)_4Si$ as the internal standard. Uv spectra were obtained on a Cary Model 14PM spectrometer.

Ethyl 5,6-Dihydro-2-oxo-2*H*-naphtho[1,2-*b*]pyran-3-carboxylate (1).—To a solution of 0.55 mol of NaOEt in 500 ml of dimethoxyethane, 84.5 g (0.5 mol) of ethyl ethoxymethylenecyanoacetate and then 73 g (0.5 mol) of α-tetralone were added dropwise. The reaction mixture was stirred overnight at room temperature and poured onto 500 ml of 3 *N* HCl. Yellow crystals were collected by filtration and washed with Me_2CO. A mixture of the crystals and 500 ml of H_2O was warmed on the

steam bath for 3 hr, cooled, and filtered to give 112.4 g (83%) of 1, mp 145–147°. Two recrystallizations (EtOH) gave an analytical sample: mp 148–149°; ir 1750 cm^{-1} (C=O); nmr (DMSO) δ 1.4 (t, 3, CH_3), 2.9 (m, 4 H), 4.35 (q, 2, OCH_2), 7.0–8.0 (m, 5 H).

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.23. Found: C, 71.16; H, 5.34.

Ethyl 8-Methoxy-5,6-dihydro-2-oxo-2*H*-naphtho[1,2-*b*]pyran-3-carboxylate (2).—6-Methoxy-α-tetralone (470 g, 2.67 mol) was converted by the procedure described above to 2, mp 141–143°. Recrystallization (DMF–H_2O) gave 550 g (68.5%) of analytically pure 2: mp 150.5–152°; ir 1750 cm^{-1} (C=O); nmr (CF_3CO_2H) δ 0.9 (t, 3, CH_3), 2.2 (s, 4 H), 3.2 (s, 3, OCH_3), 4.0 (q, 2, OCH_2), 6.4–7.4 (m, 3 H), 8.0 (s, 1 H).

Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.76; H, 5.43.

2,3,4,4a,9,10-Hexahydro-2,4a-ethanophenanthrene-2-carboxylic Acid (7).—The pyran 1 (50 g, 0.185 mol) was allowed to react with ethylene at 3000 atm at 200° for 14 hr to give 47.3 g (91%) of 5, mp 50–51°, ir 1730 cm^{-1} (C=O). A mixture of 7 g (24.8 mmol) of 5 an 125 ml of 2 *N* NaOH was heated at reflux for 12 hr, cooled, washed twice with Et_2O, and acidified with concentrated hydrochloric acid to give 5.77 g (92%) of 7, mp 217–225°. One recrystallization (EtOH) gave an analytical sample: mp 227–228°; ir 1700 cm^{-1} (C=O); nmr (DMSO) δ 1.3 (m, 4 H), 2.0 (m, 4 H), 2.5 (m, 4 H), 6.2 (s, 1 H), 7.3 (m, 4 H).

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.12. Found: C, 80.06; H, 6.86.

Ethyl 8-Methoxy-2,3,4,4a,9,10-hexahydro-2,4a-ethanophenanthrene-2-carboxylate (6).—Similarly, 82.5 g (0.275 mol) of the pyran 2 gave with ethylene 73 g (85%) of colorless crystals (EtOH) of 6, mp 92–92.5°, ir 1725 cm^{-1} (C=O).

Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 77.17; H, 7.81.

3,4,9,10-Tetrahydrophenanthrene-2-carboxylic Acid (4).—The pyran 1 (10 g, 37 mmol) was allowed to react with ethylene at 1000 atm at 200° for 14 hr to give 9 g (96%) of a reddish oil 3, ir 1700 cm^{-1} (C=O). The oil was hydrolyzed with 2 *N* NaOH to give 6.55 g (74%) of 4, mp 184–186°. One recrystallization (EtOH) gave an analytical sample: mp 188–189°; ir 1775 cm^{-1} (C=O); uv (EtOH) 353 nm (ε 19,600); nmr (DMSO) δ 2.5 (m, 8 H), 7.0 (s, 1 H), 7.2 (m, 4 H).

Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.99; H, 6.25.

7-Methoxy-2,3,4,4a,9,10-hexahydro-2,4a-ethanophenanthrene-2-carboxylic Acid (8).—A mixture of 460 g (1.47 mol) of 6, 80 g (2 mol) of NaOH, and 1000 ml of diethylene glycol was heated at 160° for 2 hr. The mixture was cooled, diluted with H_2O, and acidified with concentrated hydrochloric acid to give 410 g (99%) of 8. One recrystallization (CH_3CN) gave an analytical sample, mp 213–216°, ir 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{18}H_{20}O_2$: C, 76.03; H, 7.09. Found: C, 76.24; H, 7.07.

1,2,3,4,4a,9,10,10a-Octahydro-2,4a-ethanophenanthrene-2-carboxylic Acid (11).—The ester 5 (25 g, 88.7 mmol) was hydrogenated in EtOH with 5% Pt–C at 3 atm at room temperature. Filtration and concentration of the filtrate gave 24.15 g (96%) of 9, mp 74–79°, ir 1730 cm^{-1} (C=O). Hydrolysis of 9 with 2 *N* NaOH gave 19.8 g (91%) of 11, mp 205–207°. One recrystallization (EtOH) gave an analytical sample: mp 209–210.5°; λ 1700 cm^{-1}; nmr (DMSO) δ 1.8 (m, 13 H), 2.75 (t, 2 H), 7.15 (m, 4 H).

Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.62; H, 7.90.

Ethyl 7-Methoxy-1,2,3,4,4a,9,10,10a-octahydro-2,4a-ethanophenanthrene-2-carboxylate (10).—A mixture of 69.6 g (0.2 mol) of 6, 200 ml of EtOAc, and 0.2 g of 10% Pd/C was hydrogenated at 50 psi and room temperature to give 70 g (100%) of 10. One recrystallization (*i*-PrOH–H_2O) gave an analytical sample, mp 65.5–67.5°, ir 1730 cm^{-1} (C=O).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.69; H, 8.40.

1,2,3,4,4a,9,10,10a-Octahydro-2,4a-ethanophenanthrene-2-amine Hydrochloride (12).—A solution of 6.0 g (23.4 mmol) of the acid 11 and 2.6 g (25.7 mmol) of Et_3N in 80 ml of Me_2CO was cooled to 0°. Maintaining this temperature, 2.8 g (25.8 mmol) of $ClCO_2Et$ was added, the reaction was stirred for 30 min, and then a solution of 3.1 g (47.7 mmol) of NaN_3 in 8 ml of H_2O was added. After the reaction mixture was stirred for an additional 30 min, it was poured onto ice and extracted with 4 × 50 ml of toluene. The combined extracts, after drying over $MgSO_4$, were gently heated until N_2 evolution ceased. Concentration under vacuum gave 5.75 g of the isocyanate, λ 2300 cm^{-1} (NCO). A solution of this isocyanate in 15 ml of methanol was stirred overnight and the solvent was removed under vacuum to yield the methyl carbamate, λ 1750 cm^{-1} (C=O). A solution of the carbamate in 100 ml of BuOH containing 11.2 g (0.2 mol) of KOH was heated at reflux overnight, then cooled and acidified with 4 *N* aqueous HCl. The acidic solution was concentrated under vacuum and the residue was twice recrystallized (H_2O) to give 1.8 g (29%) of 12, λ 3300 cm^{-1} (NH_3), nmr (D_2O) δ 1.8 (m, 13 H), 2.75 (t, 2 H), 7.2 (m, 4 H).

Anal. Calcd for $C_{16}H_{21}N \cdot HCl \cdot {}^1/_2H_2O$: C, 70.18; H, 8.46; N, 5.12; Cl, 12.95. Found: C, 70.44; H, 8.46; N, 5.07; Cl, 12.94.

Registry No.—1, 23716-45-2; 2, 32497-39-5; 4, 39253-61-7; 5, 23716-46-3; 6, 32497-41-9; 7, 23718-15-2; 8, 32497-43-1; 9, 23716-47-4; 10, 32497-42-0; 11, 23716-48-5; 12, 23716-49-6; ethyl ethoxymethylenecyanoacetate, 94-05-3; α-tetralone, 529-34-0; 6-methoxy-α-tetralone, 1078-19-9.

A New Synthesis of α-Amino Acids[1]

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Received December 28, 1972

A number of methods for the practical chemical synthesis of α-amino acids exist,[2] among which the amination of carboxylic acids figures prominently. For example, amination of α-halogen acids[3] and unsaturated esters[4] and reductive amination of α-keto acids[5] is frequently employed. Recently, Inouye, *et al.*, reported the amination of sodiomalonate by chloramine[6] and Yamada, *et al.*, have described a similar amination of α-lithiated carboxylic acid salts by various aminating reagents.[7] However, the carboxylation of the α-carbon atom of amines has not been reported previously.

Within the framework of our studies on the synthesis of amino acids, we have studied the reaction of isocyano compounds with various electrophiles.[8–10] In the present paper, we wish to report a new synthesis of α-amino acids by α-carboxylation of isocyano compounds, which are easily prepared from the corresponding amines.[11]

(1) Synthesis of Amino Acids and Related Compounds. 4. Part 3: ref 10. The present study was presented at the 22nd Meeting of the Kinki Branch of the Pharmaceutical Society of Japan, Hyogo, Nov. 12, 1972.

(2) For example, J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Wiley, New York, N. Y., 1961, p 697.

(3) A. Cahours, *C. R. Acad. Sci.*, **46**, 1044 (1858); *Justus Liebigs Ann. Chem.*, **109**, 10 (1859).

(4) R. Engel, *Bull. Soc. Chim. Fr.*, **48**, 97 (1887).

(5) E. Erlenmeyer, *Justus Liebigs Ann. Chem.*, **271**, 137 (1892).

(6) M. Horiike, J. Oda, Y. Inouye, and M. Ohno, *Agr. Biol. Chem.*, **33**, 292 (1969).

(7) S. Yamada, T. Oguri, and T. Shioiri, *Chem. Commun.*, 623 (1972).

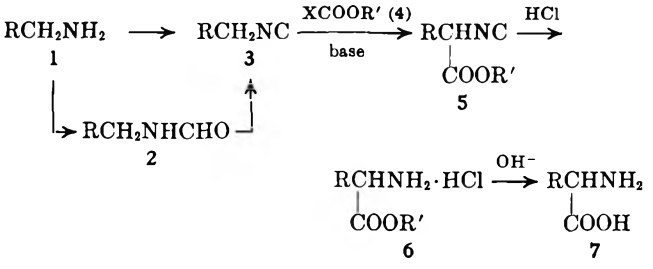
(8) M. Suzuki, K. Matsumoto, T. Iwasaki, and K. Okumura, *Chem. Ind. (London)*, 687 (1972).

(9) M. Suzuki, T. Iwasaki, K. Matsumoto, and K. Okumura, *Syn. Commun.*, **2**, 237 (1972).

(10) M. Suzuki, T. Iwasaki, K. Matsumoto, and K. Okumura, *Chem. Ind. (London)*, in press.

(11) After the work described in this note was completed, we became aware of a report by W. Vaalburg, J. Strating, M. G. Woldring, and H. Wynberg, *Syn. Commun.*, **2**, 423 (1972), who prepared α-phenylglycine by the same method.

The α-carboxylation of isocyano compounds was carried out according to the following scheme. The isocyano compounds (**3**) were prepared according to an improved Hofmann carbylamine reaction[12] or the Ugi reaction, which consists of the dehydration of N-monosubstituted formamides (**2**) using phosgene in the presence of tertiary amines.[13]



When the various isocyanides (**3**) reacted with diethyl carbonate in the presence of sodium hydride in dimethylformamide, ethoxycarbonylation proceeded easily at the α carbon of the isocyanides, and the corresponding ethyl α-isocyanoacetate derivatives (**5**, R′ = Et) were obtained in 59–63% yields as listed in Table I.[14–17] The ir spectra of these compounds showed the characteristic absorption of the isonitrile group at 2130–2145 cm^{-1} and of the ester group at 1740–1755 cm^{-1}, respectively, and the nmr spectra showed one proton signal for the methine near δ 5.20. The isonitrile group of the ethyl α-isocyanoacetate derivatives was converted to the amino group by partial hydrolysis with dilute hydrochloric acid, giving the amino acid ester hydrochlorides (**6**, R′ = Et). Subsequently, the resulting compounds were hydrolyzed in sodium hydroxide solution and the corresponding free amino acids (**7**) were obtained by adjusting the pH to the isoelectric point with concentrated hydrochloric acid or by treatment with an ion exchange resin. The amino acids obtained were homogeneous by paper partition chromatography (PPC) and electrophoresis (EP) criteria and possessed the physicochemical properties of an authentic specimen.

Table I
Formation of α-Amino Acids[a]

3	5 (R′ = Et) Ir, cm^{-1}	Nmr,[b]	Yield,	7[c]	Yield,[d]
R	NC, COOEt	δ	%	Mp, °C	%
Ph	2130, 1752	5.22	63	256 sub[e,f]	57
4-CH_3OPh	2135, 1755	5.19	60	264–267 sub[g]	54
4-CH_3Ph	2145, 1750	5.20	59	268–270 sub[h]	51
4-ClPh	2130, 1740	5.25	62	267–270 dec[i]	56
3,4-Methylenedioxy Ph	2140, 1750	5.16	63	227–229 sub[j]	60
2-Furyl	2130, 1745	5.31	61	209–211	55
H[k]	2150, 1755		35	235–237 dec[l]	32

[a] Reaction of isocyano compounds with diethyl carbonate in the presence of NaH. [b] Methine (s) in CCl_4. [c] Analyses agreed with the calculated values within ±0.3%. [d] Total yield from **3**. [e] sub: sublimation. [f] Lit.[14] reports sub without melting at 256°. [g] Lit.[15] mp 264–266° sub. [h] Lit.[15] mp 260–265° sub. [i] Lit.[15] mp 269–271° dec. [j] Lit.[16] mp 210°. [k] BuLi was used. [l] Lit.[17] mp 237° dec.

We have also studied various carboxylating reagents other than diethyl carbonate, *e.g.*, dimethyl carbonate, carbon dioxide, ethyl chloroformate, and diethyl oxalate. In the case of dimethyl carbonate, the methoxycarbonylation proceeded in 70% yield under the same conditions as diethyl carbonate. Although the reaction with carbon dioxide or ethyl chloroformate did not proceed in the presence of sodium hydride, the use of *n*-butyllithium as a base promoted the carboxylation of benzyl isocyanide in 35–40% yield. However, the carboxylation with diethyl oxalate did not occur under the same conditions described above. These results are summarized in Table II. This procedure was extended to the alkyl isocyanide. Glycine was obtained from methyl isocyanide (Table I) but the expected product was not obtained from *n*-butyl isocyanide.

Table II
Carboxylations with Various Reagents

$$PhCH_2NC + XCOOR \xrightarrow{\text{base}} PhCH(NC)COOR$$

X	R	Base	Reaction conditions			Yield, %
EtO	Et	NaH	DMF	[b]	1 hr	63
MeO	Me	NaH	DMF	[b]	1 hr	70
CO_2		BuLi	THF	−50°	1 hr	40[a]
Cl	Et	BuLi	THF	−50°	1 hr	35
COOEt	Et	BuLi	THF	−50°	1 hr	0

[a] Total yield of phenylglycine by hydrolysis. [b] Room temperature.

It appears that this synthetic method will be practically useful on a large scale when easily obtainable primary amines are used.

Experimental Section[18]

Materials.—Isocyanides (**3**) were prepared according to the method described by Weber, *et al.*,[12] or Ugi, *et al.*:[13] benzyl isocyanide, bp 92–93° (11 mm); 4-methoxybenzyl isocyanide, bp 114–115° (5 mm); *p*-xylyl isocyanide, bp 80–81° (3 mm); 4-chlorobenzyl isocyanide, bp 79–80° (5 mm); 3,4-methylenedioxybenzyl isocyanide, bp 120–121° (4 mm); 2-furylmethyl isocyanide, bp 85–87° (50 mm); methyl isocyanide, bp 25–30° (150 mm).

General Procedure of α-Carboxylations. A. Reaction of Isocyano Compounds with Diethyl Carbonate.—A mixture of 2.34 g (0.02 mol) of benzyl isocyanide and 2.36 g (0.02 mol) of diethyl carbonate in 10 ml of dimethylformamide was gradually added to a suspension of 0.84 g (0.022 mol) of sodium hydride (63% in oil) in 15 ml of dimethylformamide at 15° over a period of 15 min under stirring. After stirring was continued for 1 hr at room temperature, the reaction mixture was neutralized with acetic acid under cooling with an ice bath and the solvent was removed under reduced pressure below 50°. The residue was extracted with ethyl acetate, and the extract was washed with water and dried over magnesium sulfate. After the solvent was evaporated *in vacuo*, the product was purified by column chromatography on silica gel (80 g, Kieselgel 0.2–0.5 mm, E. Merck). After the paraffin included in sodium hydride was removed by elution with *n*-hexane, 2.38 g of ethyl α-isocyanophenylacetate was eluted with benzene (63% yield): ir (film) 2130 (NC), 1752 cm^{-1} (COOEt); nmr (CCl_4) δ 7.40 (s, 5, ArH), 5.22 (s, 1, CH), 4.18 (q, 2, CH_2), 1.23 (t, 3, CH_3).

(12) W. P. Weber and G. W. Gokel, *Tetrahedron Lett.*, 1637 (1972).
(13) I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, and K. Offermann, *Angew. Chem.*, **77**, 492 (1965).
(14) F. Tiemann, *Ber.*, **13**, 381 (1880).
(15) F. P. Doyle, G. R. Fosker, J. H. C. Nayler, and H. Smith, *J. Chem. Soc.*, 1440 (1962).
(16) C. Lorenz, *Ber.*, **14**, 785 (1881).
(17) M. Orten and R. M. Hill, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 300.

(18) Melting points and boiling points are uncorrected. Melting points were measured by the use of the Yamato melting point apparatus. Infrared spectra were recorded on a Shimadzu IR-27G infrared spectrophotometer. Nmr spectra were obtained using a Hitachi Perkin-Elmer R-20A high-resolution nmr spectrometer with tetramethylsilane as internal standard. The R_f value on PPC was recorded using Toyo filter paper No. 51.

Various α-isocyanoacetic acid derivatives (5, R′ = Et) were prepared by the same conditions and procedure. The yields, ir, and nmr spectra of these compounds are summarized in Table I.

Hydrolysis of the ethyl α-isocyanoacetate derivatives (5, R′ = Et) was carried out as follows: 1.89 g (0.01 mol) of the ethyl α-isocyanophenylacetate was dissolved in a mixture of hydrochloric acid (6 ml) and methanol (30 ml), and the mixture was heated at 50° for 30 min to convert the isonitrile group to the amino group. After the reaction was complete, the solvent and the excess hydrochloric acid were removed *in vacuo*. The resulting hydrochloride was dissolved without purification in 20 ml of 2 *N* sodium hydroxide and allowed to stand for 3 hr at room temperature. The reaction mixture was washed with ether and decolorized with activated charcoal. Subsequently, the alkaline solution was adjusted to pH 6.5 with concentrated hydrochloric acid and the mixture was allowed to stand overnight in an ice box. The precipitate was collected by filtration and dried; 1.36 g of phenylglycine was obtained (90% yield). The compound showed a single spot on PPC, R_f 0.40 (*n*-BuOH:AcOH:H_2O, 3:1:1).

Anal. Calcd for $C_8H_9O_2N$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.43; H, 6.11; N, 9.18.

Part of the ethyl α-isocyanoacetate derivatives (5, R′ = Et) was converted to the amino acid ethyl ester hydrochlorides (6, R′ = Et) by partial acid hydrolysis in the same way as above. For example, from 0.95 g (0.005 mol) of ethyl α-isocyanophenylacetate, 1.04 g of phenylglycine ethyl ester hydrochloride was obtained (97% yield), mp 203° dec (lit.[19] mp 197° dec).

B. Reaction of Benzyl Isocyanide with Dimethyl Carbonate.—A mixture of 2.34 g (0.02 mol) of benzyl isocyanide and 1.80 g (0.02 mol) of dimethyl carbonate in 10 ml of dimethylformamide was gradually added to a suspension of 0.84 g (0.002 mol) of sodium hydride (63% in oil) in 15 ml of dimethylformamide at 15° over a period of 15 min under stirring. Stirring was continued for 1 hr at room temperature, the treatment was carried out according to method A, and 2.45 g of methyl α-isocyanophenylacetate was obtained (70% yield): ir (film) 2130 (NC), 1750 cm^{-1} (COOMe); nmr (CCl_4) δ 7.40 (s, 5, ArH), 5.29 (s, 1, CH), 3.70 (s, 3, OMe).

C. Reaction of Benzyl Isocyanide with Carbon Dioxide.—To a solution of 2.34 g (0.02 mol) of benzyl isocyanide in 15 ml of tetrahydrofuran was added dropwise a mixture of 13 ml of *n*-butyllithium (15% in hexane) in 8 ml of tetrahydrofuran at −60° over a period of 30 min under stirring. Stirring was continued for 1 hr at the same temperature, 1.76 g (0.04 mol) of Dry Ice was added to the reaction mixture, and the mixture was gradually warmed to 0°. Hydrochloric acid was added to the mixture to bring the pH to about 2 and the mixture was heated at 50° for 30 min and then evaporated under reduced pressure. To the residue was added water, and the solution was washed with ether and subsequently concentrated *in vacuo*. The hydrolyzed products were dissolved in 15 ml of water and treated with a Dowex 50 column (H^+ form) and the acidic components, but not the amino acids, were eluted with water. The amino acid was eluted with 5% ammonia. The solution was concentrated to dryness under reduced pressure and 1.21 g of phenylglycine identical with an authentic specimen was obtained (40% yield).

D. Reaction of Benzyl Isocyanide with Ethyl Chloroformate.—To a solution of 2.34 g (0.02 mol) of benzyl isocyanide in 15 ml of tetrahydrofuran was added dropwise a mixture of 13 ml of *n*-butyllithium (15% in hexane) in 8 ml of tetrahydrofuran at −60° over a period of 30 min under stirring. After stirring was continued for 1 hr at the same temperature, 2.17 g (0.02 mol) of ethyl chloroformate was added to the reaction mixture and then the mixture was gradually warmed to 0°. The mixture was neutralized with acetic acid and the solvent was removed under reduced pressure. The residue was extracted with ethyl acetate, and the extract was washed with water, dried over magnesium sulfate, and evaporated *in vacuo*. The product was purified by column chromatography of silica gel (80 g, Kieselgel 0.2–0.5 mm, E. Merck); 1.17 g of ethyl α-isocyanophenylacetate was obtained by elution with benzene (35% yield).

E. Reaction of Methyl Isocyanide with Diethyl Carbonate.—To a solution of 0.82 g (0.02 mol) of methyl isocyanide in 15 ml of tetrahydrofuran was added dropwise a mixture of 13 ml of *n*-butyllithium (15% in hexane) in 8 ml of tetrahydrofuran at −60° over a period of 30 min under stirring. After stirring was continued for 1 hr at the same temperature, 2.36 g (0.02 mol) of diethyl carbonate was added to the reaction mixture and then the mixture was gradually warmed to 0°. The treatment was carried out according to method D; 0.79 g of ethyl α-isocyanoacetate was obtained (35% yield). Glycine was prepared from this compound by the usual hydrolysis in 32% overall yield.

Registry No.—**3** (R = Ph), 10340-95-7; **3** (R = H), 593-75-9; **3** (R = 4-CH_3OPh), 1197-58-6; **3** (R = 4-CH_3Ph), 39495-97-1; **3** (R = 4-ClPh), 39546-47-9; **3** (R = 3,4-methylenedioxy Ph), 39533-29-4; **3** (R = 2-furyl), 2920-07-2; **5** (R = Ph; R′ = Et), 39533-31-8; **5** (R = Ph; R′ = Me), 39533-32-9; **5** (R = 4-CH_3OPh; R′ = Et), 39533-33-0; **5** (R = 4-CH_3Ph; R′ = Et), 39533-34-1; **5** (R = 4-ClPh; R′ = Et), 39533-35-2; **5** (R = 3,4-methylenedioxy Ph; R′ = Et), 39533-36-3; **5** (R = 2-furyl; R′ = Et), 39533-37-4; **5** (R = H; R′ = Et), 2999-46-4; **6** (R = Ph; R′ = Et), 879-48-1; **7** (R = Ph), 69-91-0; **7** (R = 4-CH_3OPh), 2540-53-6; **7** (R = 4-CH_3Ph), 13227-01-5; **7** (R = 4-ClPh), 6212-33-5; **7** (R = 3,4-methylenedioxy Ph), 39533-43-2; **7** (R = 2-furyl), 17119-54-9; **7** (R = H), 56-40-6; diethyl carbonate, 105-58-8; dimethyl carbonate, 616-38-6; carbon dioxide, 124-38-9; ethyl chloroformate, 541-41-3.

Acknowledgment.—We wish to express our thanks to Drs. T. Takayanagi and I. Chibata for their encouragement in this study.

(19) A. Kossel, *Ber.*, **24**, 4145 (1891).

An Improved Synthesis of 4-Methyl- and 4,5-Dimethyl-3-pentadecylcatechol

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Interest in the synthesis of various ring derivatives and homologs of 3-pentadecylcatechol, the saturated component of the poison ivy allergenic principle, has recently developed as the result of clinical observations concerning the immunologic and toleragenic activity of such compounds.[1-3] Because of their potential effectiveness in blocking nucleophilic reactions of the quinone of 3-pentadecylcatechol, the several ring-substituted methyl derivatives of 3-pentadecylcatechol have been of particular interest. Their syntheses, recently reported from these laboratories,[2,3] have involved in several instances multistep routes leading to low overall yields (in the range of 10–15%). We wish now to report a much improved method (three-step, overall yield about 50–55%) for the synthesis of 4-methyl- and 4,5-dimethyl-3-pentadecylcatechol (**2a** and **2b**).

The improved route starts with the benzylation of 3-pentadecylcatechol[4] according to the procedure of

(1) H. Baer, C. R. Dawson, J. S. Byck, and A. P. Kurtz, *J. Immunol.*, **104**, 178 (1970).

(2) J. S. Byck and C. R. Dawson, *J. Org. Chem.*, **32**, 1084 (1967).

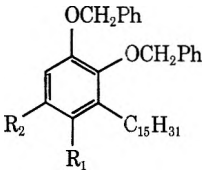
(3) J. S. Byck and C. R. Dawson, *J. Org. Chem.*, **33**, 2451 (1968).

(4) The 3-pentadecylcatechol was obtained according to the method of Kurtz and Dawson, *J. Med. Chem.*, **14**, 729 (1971).

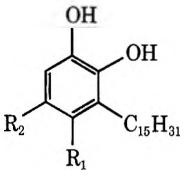
Loev and Dawson[5] and then chloromethylation of the dibenzyl ether **1a**. Earlier exploratory studies by Byck had indicated that chloromethylation leads to the formation of a monochloromethylated product.[6] In the present investigation we have thoroughly studied this reaction and have found that depending upon the proper conditions, either one or two chloromethyl groups can be introduced on the aromatic nucleus.

If the chloromethylation of **1a** is carried out with the passage of hydrogen chloride for 2 hr at 0° the product is 4-chloromethyl-3-pentadecylcatechol dibenzyl ether (**1b**). If, however, hydrogen chloride is allowed to pass through the reaction mixture for 6 hr at room temperature, then dichloromethylation is achieved, and the resulting product is 4,5-bis(chloromethyl)-3-pentadecylcatechol dibenzyl ether (**1c**). Infrared and nmr spectra have indicated that partial debenzylation occurs in the latter reaction. Since this does not interfere with the final step, no attempt was made to purify **1c**.

Both the mono- and dichloromethylated products can now be conveniently converted to 4-methyl-3-pentadecylcatechol (**2a**) and 4,5-dimethyl-3-pentadecylcatechol (**2b**), respectively, by hydrogenation with a 10% palladium on carbon catalyst. The structure of the hydrogenolysis products, as documented in the Experimental Section, verifies that the chloromethylation of **1a** can be made to give either **1b** or **1c**. This scheme thus provides a much simplified route of synthesis and an improved yield of several methylated analogs of 3-pentadecylcatechol.



1a, $R_1 = R_2 = H$
b, $R_1 = CH_2Cl$; $R_2 = H$
c, $R_1 = R_2 = CH_2Cl$



2a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = R_2 = CH_3$

Experimental Section[7]

4-Chloromethyl-3-pentadecylcatechol Dibenzyl Ether (1b).—A sample of 10.0 g (0.02 mol) of benzylated 3-pentadecylcatechol (**1a**), mp 51.0–52.0° (lit.[5] mp 52.4–53.0°), 7.4 g of paraformaldehyde, 54 ml of benzene, and 54 ml of acetic acid were cooled in an ice bath, and dry hydrogen chloride was passed through the mixture with continuous stirring. After 45 min the solution became clear, and the hydrogen chloride passage was continued for an additional 2 hr. Water and ether were added, the phases were separated, and a conventional work-up was performed. The residue was recrystallized twice from hexane to give 8.2 g (75%) of a white solid (**1b**): mp 50.0–51.0°; nmr (CCl_4) τ 2.7 (s, 10 H, C_6H_5–), 3.1 (q, 2 H, aromatic), 4.9 (s, 4 H, OCH_2–), 5.5 (s, 2 H, $-CH_2Cl$), 7.4 (t, 2 H, benzylic), 8.7 (broad s, CH_2), 8.9–9.1 (t, terminal Me), signals at 8.6–9.2 integrated for 29 H; mass spectrum m/e 549 (M^+).

4,5-Bis(chloromethyl)-3-pentadecylcatechol Dibenzyl Ether (1c).—Samples of 10.0 g of **1a**, 7.4 g of paraformaldehyde, 54 ml of benzene, and 54 ml of acetic acid were mixed in an ice bath and hydrogen chloride was passed through the mixture for 0.5 hr. The ice bath was removed and passage of hydrogen chloride was continued for 6 hr at room temperature. Water and ether were added, the phases were separated, and a conventional work-up was performed. The residue was recrystallized from hexane to yield 8.36 g (70%) of a white solid (**1c**): mp 79.0–81.0°; ir (CCl_4) 2.86 μ (w, OH, indicating partial debenzylation had occurred); nmr (CCl_4) τ 2.6 (s, 8 H, C_6H_5–), 3.2 (s, 1 H, aromatic), 4.3 (broad s, minor, OH, resulting from partial debenzylation), 4.9 (s, 3 H, OCH_2–), 5.2–5.3 (d, 4 H, $-CH_2Cl$), 7.4 (t, 2 H, benzylic), 8.7 (broad s, CH_2), 8.9–9.1 (t, terminal Me), signals at τ 8.6–9.2 integrated for 29 H.

4-Methyl-3-pentadecylcatechol (2a).—A sample of 5.5 g (0.01 mol) of **1b** was dissolved in 100 ml of ethyl acetate containing 2 drops of sulfuric acid, and the solution was hydrogenated in a Parr pressure reaction apparatus for 6 hr over 0.3 g of 10% palladium on carbon catalyst at an initial hydrogen pressure of 60.0 psi and at room temperature. The catalyst was then removed by filtration, and the solution was diluted with ether and washed with 10% sodium bicarbonate followed by water. The residual oil obtained after drying the solution and removal of solvent was recrystallized several times from ligroin to give 3.18 g (95%) of **2a**. This compound was identical in melting point (55.0–56.0°) and spectra (ir and nmr) with an authentic sample of 4-methyl-3-pentadecylcatechol.[3]

4,5-Dimethyl-3-pentadecylcatechol (2b).—An identical hydrogenolysis procedure was performed on 6.0 g (0.01 mol) of **1c**. The residual oil obtained after the work-up was recrystallized from hexane to yield 3.17 g (91%) of **2b**. This compound was identical in melting point and spectra (ir and nmr) with an authentic sample of 4,5-dimethyl-3-pentadecylcatechol.[2]

Registry No.—**1a**, 2792-00-9; **1b**, 39533-51-2; **1c**, 39533-52-3; **2a**, 16273-11-3; **2b**, 7771-22-4.

Acknowledgment.—This investigation was supported in part by Contract PH-43-64-76 with the Division of of Biologics Standards of the National Institutes of Health.

(5) B. Loev, and C. R. Dawson, *J. Amer. Chem. Soc.*, **78**, 6095 (1956).

(6) J. S. Byck, laboratory notes, Columbia University, 1967.

(7) Melting points were measured on a Thomas-Hoover apparatus and are corrected. The infrared spectra were recorded on a Perkin-Elmer Infracord Model 137. The nmr spectra were run on a Varian T-60 instrument and employing 20–50% solutions in CCl_4 with a drop of TMS as internal standard. Mass spectra were obtained using a Perkin-Elmer Hitachi RMU-6d instrument.

The Reaction of Trimethylsilyl Enol Ethers with Simmons–Smith Reagent. A Facile Synthesis of Trimethylsilyl Cyclopropyl Ethers and Cyclopropanols

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The reaction of trimethylsilyl enol ethers,[1] (**1**) with Simmons–Smith reagent[2] followed by cold, rapid work-up (method A) affords a mixture of trimethylsilyl cyclopropyl ethers (**2**) and cyclopropanols (**3**) enriched in **2**. Work-up at ambient conditions with no emphasis placed on rapid manipulation (method B) leads to a mixture of **2** and **3** enriched in **3**. The ether **2** upon treatment with aqueous acid gives **3** in good yield. These findings are outlined below in Scheme I, and representative yields are given in Table I.

Structural proof for the ethers **2** rests mainly on the spectral data of the compounds. Each ether **2** shows a characteristic nmr peak at *ca.* δ 0.05 representing the $Si(CH_3)_3$ moiety. The ir of **2** indicates that no OH grouping is present, and absorptions at 1250 and

(1) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).

(2) (a) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **81**, 4256 (1959); (b) E. LeGoff, *J. Org. Chem.*, **29**, 2048 (1964).

SCHEME I

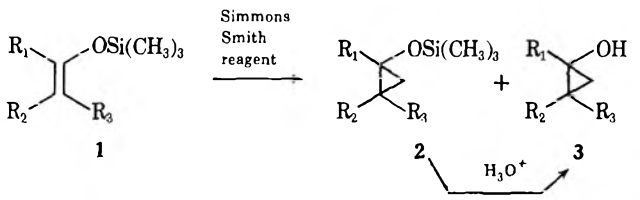
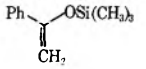
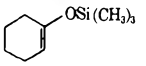
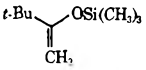
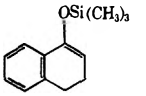


TABLE I

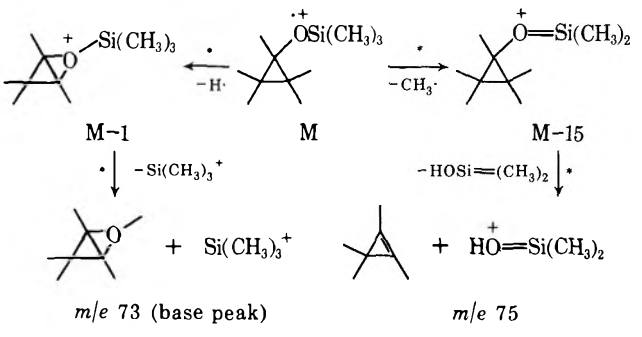
REACTION OF TRIMETHYLSILYL ENOL ETHERS WITH SIMMONS–SMITH REAGENT[a–c]

Trimethylsilyl enol ether 1	Method	2, %	Method	3, %
	A	67	A	10
	B	4 (2a)	B	73 (3a)
	A	18 (2b)	A	37 (3b)
	B	Trace	B	78
	A	57 (2c)	A	10 (3c)
	A	58 (2d)	A	20 (3d)

[a] Fast, cold work-up (method A). [b] Slow, ambient work-up (method B). [c] All compounds give ir, nmr, and mass spectral data in accord with the proposed structures.

840 cm^{-1} are diagnostic for $Si(CH_3)_3$.[3] Perhaps the clearest information concerning the structure of the ethers **2** comes from the mass spectra. The generalized fragmentation pattern is shown in Scheme II.

SCHEME II

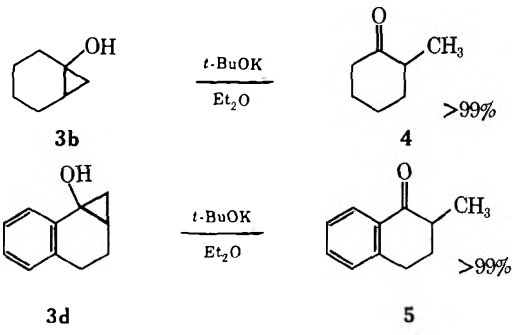


* = metastable transition

All the ethers **2** have a base peak at *m/e* 73 [$^+Si(CH_3)_3$] with intense peaks at *m/e* 75 [$HO{=}Si(CH_3)_2^+$], M − 15 ($-CH_3\cdot$), and M − 1 ($-H\cdot$). The proposed mode of fragmentation is verified by the appearance of metastable transitions between the fragments indicated. Spectral evidence for the structures of the cyclopropanols **3** is also consistant with the proposed formulations.

Chemical evidence for the structure of cyclopropanols **3b** and **3d** was obtained by a study of their reaction with potassium *tert*-butoxide. The results of this study are in agreement with those obtained by DePuy,[4] as we observed only the formation of α-methyl ketones **4** and **5**. These observations, outlined below in Scheme III, not only verify the structures

SCHEME III



3b and **3d** but are illustrative of an efficient method for the introduction of a methyl group α to a keto function. Since the conversion of **2** into **3** has been shown to be feasible, the production of the α-methyl ketones serves as structural proof for the ethers **2**.

We are attempting to extend the scope of the addition reaction to include trimethylsilyl ketene ketals and trimethylsilyl phenols.[5]

Experimental Section

General Procedure for the Reaction of Simmons–Smith Reagent with Trimethylsilyl Enol Ethers.[2b]—To a stirred, refluxing slurry of 0.02 mol of zinc–copper couple, under nitrogen, in 20 ml of dry ether containing a trace of diiodomethane, was added a solution of 0.01 mol of trimethylsilyl enol ether and 0.014 mol of diiodomethane in 10 ml of dry ether. After the addition was complete (*ca* 0.5 hr), the resulting mixture was refluxed for 20–24 hr. After cooling, the reaction mixture was worked up in the following manner.

Method A. Isolation of Trimethylsilyl Cyclopropyl Ethers.—The cooled reaction mixture was filtered through a plug of glass wool and immediately diluted with 25 ml of cold 10% hydrochloric acid. The layers were separated and the aqueous portion was rapidly extracted with 2 × 20 ml of cold ether. The combined ethereal extracts were then washed successively and rapidly with 20 ml of cold 10% hydrochloric acid and 2 × 20 ml of cold water. After drying over anhydrous magnesium sulfate, the ethereal solution was filtered and solvent was removed *in vacuo* to afford a mixture of **2** and **3** which was enriched in trimethylsilyl cyclopropyl ethers **2**. Column chromatography on 0.5–0.2 mesh silica gel utilizing hexane–ether mixtures as eluting solvent gave pure **2** and **3** as judged by spectral and tlc (silica gel 7G, hexane–ether mixtures) data.

Method B. Isolation of Cyclopropanols.—The same procedure outlined in method A was followed, except that all manipulations were carried out with reagents and solvents at ambient temperature, and no emphasis was placed on rapid extractions.

Conversion of Trimethylsilyl Cyclopropyl Ether 2d into Cyclopropanol 3d.—A solution of 1.16 g (5.0 mmol) of **2d** in 25 ml of ether was stirred for 0.5 hr at room temperature with 25 ml of 10% hydrochloric acid (under nitrogen). The acid was then removed and the ethereal solution was washed with 25 ml of water and dried over anhydrous magnesium sulfate. Filtration and removal of solvent *in vacuo* gave a solid residue, which was crystallized from pentane to afford 0.48 g (60%) of cyclopropanol **3d**, mp 100–104°. The nmr and ir of synthetic **3d** were identical with those of authentic **3d**, and the tlc behavior of synthetic **3d** was identical with that of authentic **3d** (silica gel 7G, hexane–ether, 4:1).

Conversion of 3b into 2-Methylcyclohexanone by Treatment with Base.—A slurry of 0.08 g (0.7 mmol) of cyclopropanol **3b** and 0.11 g (1.0 mmol) of potassium *tert*-butoxide in 10 ml of dry ether was refluxed overnight with stirring under a nitrogen atmosphere. After cooling, the mixture was diluted with 1 ml of water and the layers were separated. The aqueous layer was extracted with 1 ml of ether and the combined ethereal solution

(3) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958.

(4) C. H. DePuy, *Accounts Chem. Res.*, **1**, 33 (1968).

(5) For a recent example of the addition of Simmons–Smith reagent to a bis(trimethylsiloxy)diene, see J. M. Denis and J. M. Conia, *Tetrahedron Lett.*, 4593 (1972).

was washed with 1 ml of water. After drying over anhydrous magnesium sulfate, the ethereal solution was filtered and solvent was removed *in vacuo* to afford 0.08 g (100%) of 2-methylcyclohexanone (4). The synthetic material was identical with an authentic sample (Columbia) as judged by identical ir, nmr, and glpc behavior (12 ft, 20% DEGS at 148°).

Registry No.—**1a**, 13735-81-4; **1b**, 6651-36-1; **1c**, 17510-46-2; **1d**, 38858-72-9; **2a**, 38858-73-0; **2b**, 38858-74-1; **2c**, 38858-75-2; **2d**, 38858-76-3; **3a**, 29526-96-3; **3b**, 34737-45-6; **3c**, 38858-79-6; **3d**, 38858-80-9.

The Synthesis of *N*-Methylhomopavine [(±)-Homoargemonine][1]

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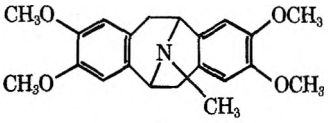
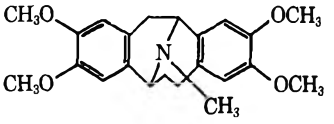
In the past 10 years a new class of poppy alkaloids, the pavine group [represented by argemonine (I)], has



I

been discovered and a number of alkaloids having varying substituent placements on the basic pavinane[2] ring structure have been described.[3] A number of the natural alkaloids as well as some simple synthetic analogs have shown[4] weak analgetic activity or toxicity in mice. Because substituent modifications on the pavinane ring structure did not lead to increased analgetic activity, we decided to modify the basic structure itself. A particularly attractive modification appeared to be one with expansion of the central ring as in (±)-homoargemonine (II), since it seems possible that II

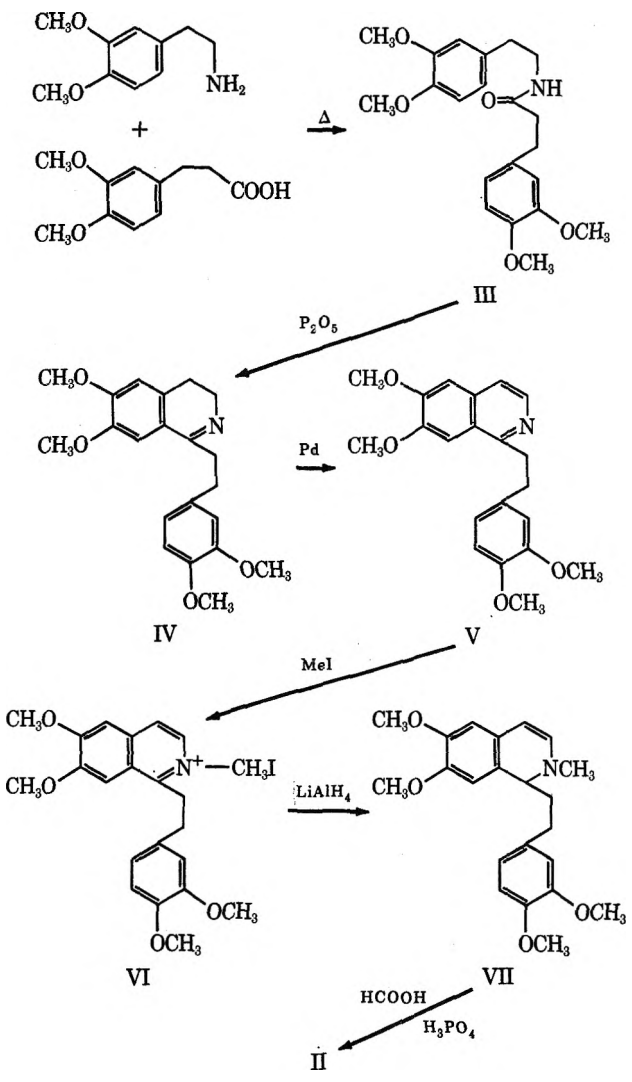


II

could also represent a member of a new, as yet undiscovered, but highly probable alkaloid class. The requisite biogenetic precursor of II would be a 1-phenethyl-1,2,3,4-tetrahydroisoquinoline. Such 1-phenethyl derivatives have now been found in nature and have also been shown to be precursors of some natural homomorphinandienones, colchicines, and similar alkaloids.[5] The structural requirements involved in the cyclization which yields I-type compounds have not been explored and the lack of II-type compounds in nature could have been ascribed to a failure in the seemingly simple extension of I biosynthesis pathways to the case of II. This note reports the ready synthesis of the new ring system exemplified by II.

The synthesis of II was accomplished by means of the reactions in Scheme I as described in the Experimental Section. Data on pharmacological activity will be published elsewhere when it is available.

SCHEME I



Experimental Section

***N*-2-(3,4-Dimethoxyphenyl)ethyl-3-(3,4-dimethoxyphenyl)propionamide (III).**—A mixture of 22.0 g of 3-(3,4-dimethoxyphenyl)propionic acid (prepared from reduction of 3,4-dimethoxycinnamic acid purchased from Aldrich) and 25 g of 2-(3,4-dimethoxyphenyl)ethylamine (Aldrich) was heated under N_2 at 190° for 2 hr. The mixture was then cooled, dissolved in ethyl acetate, and washed with dilute HCl, dilute NaOH, and water in that order. The solvent was then removed and the product was recrystallized from ethanol to give 30 g (77%) of amide as a white solid, mp 99° (lit.[6] mp 99–100°).

1-(3,4-Dimethoxyphenethyl)-6,7-dimethoxyisoquinoline (V).—The amide (25 g) was dissolved in 250 ml of dry toluene, 125 g of P_2O_5 was added, and the mixture was refluxed for 1 hr under N_2. After the mixture cooled, the excess P_2O_5 was decomposed by the addition of ice and the toluene was extracted with three 50-ml portions of warm water. The aqueous extracts were cooled and taken to pH 10 with cold NaOH solution. The basic mixture

(1) Part XVIII in the series "Alkaloids of the Papaveraceae." For part XVII see L. L. Miller, F. R. Stermitz, and J. R. Falck, *J. Amer. Chem. Soc.*, in press. This work was supported in part by Grant GM-19234 from the National Institute of General Medical Sciences, U. S. Public Health Service, and in part by Vipont Chemical Co.

(2) C. H. Chen and T. O. Soine, *J. Pharm. Sci.*, **61**, 55 (1972).

(3) F. Santavy in "The Alkaloids," Vol. XII, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1970, p 370.

(4) Unpublished results from our laboratories with A. E. Jacobson, L. B. Kier, and T. O. Soine, *J. Amer. Pharm. Assoc.*, **49**, 187 (1960).

(5) I. D. Spencer in "Chemistry of the Alkaloids," S. W. Pelletier, Ed., Van Nostrand-Reinhold, Princeton, N. J., 1970, Chapter 21.

(6) S. Sagawa and H. Yoshikawa, *J. Chem. Soc.*, 1583 (1933).

was then extracted with three 75-ml portions of chloroform. The chloroform extracts were dried with K_2CO_3 and evaporated to leave the 3,4-dihydroisoquinoline IV as an oily residue. To this residue was added 100 ml of diphenyl ether and 2 g of palladium black. The mixture was heated with gentle stirring under nitrogen at 200° for 2 hr and was then diluted with benzene. The catalyst was removed by filtration and the filtrate was extracted with five 25-ml portions of 10 *M* HCl. The aqueous layer was made basic with cold NaOH solution and extracted with three 30-ml portions of chloroform. The chloroform extracts were dried with K_2CO_3 and evaporated to dryness and the resulting white solid was recrystallized from ethanol to yield 1-(3,4-dimethoxyphenethyl)-6,7-dimethoxyisoquinoline (V), 19 g (80%), mp 147° (lit.[7] mp 147°).

(±)-Homoargemonine (6,11,12,13-Tetrahydro-2,3,8,9-tetramethoxy-14-methyl-5*H*-dibenzo[*a*,*e*]cyclononene-5,11-imine)(II).—V (14 g) was methylated with methyl iodide (60 ml) in 50 ml of methanol to yield 15 g of the *N*-methiodide VI. *N*-Methiodide VI was dried and was added to 2 g of $LiAlH_4$ in dry ether (250 ml). The mixture was stirred at room temperature for 3 hr and the excess $LiAlH_4$ was then decomposed by the addition of wet ether followed by a saturated solution of sodium potassium tartrate. The aqueous layer was further washed with ether (2 × 50 ml) and the ether portions were combined, dried with K_2CO_3, and evaporated to dryness to yield 1-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-1,2-dihydro-2-methylisoquinoline, VII, as a yellow oil. This was then refluxed under N_2 with 100 ml of 7:5 HCOOH–H_3PO_4 for 8 hr. The reaction mixture was then diluted with water, washed with $CHCl_3$, made basic with NaOH solution, and extracted with three 50-ml portions of chloroform. The chloroform extract was dried with K_2CO_3 and evaporated to yield 9 g of brown oil. The oil was shown by tlc to be composed of two products. Column chromatography (Florisil 60–100 mesh) was used to separate the two products. The column yielded 2 g of a substance indicated by nmr and tlc to be 1-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 6 g of (±)-homoargemonine (II): mp 196° (ethanol); uv (CH_3OH) λ_{max} 277 nm (log ϵ 3.53); nmr ($CDCl_3$) δ 6.67–6.5 (m, 4 H, aromatic protons), 3.90 (s, 6 H, OCH_3), 3.85 (s, 6 H, OCH_3), 2.53 (s, 3 H, NCH_3), 4.23–2.37 (m, 8 H, ring CH and CH_2); mass spectrum (70 eV) *m/e* (rel intensity) 369 (45), 204 (100), 218 (11), 368 (54).

Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.50; H, 7.65; N, 4.10.

Registry No.—II, 39013-26-8; III, 20944-13-2; IV, 20944-14-3; V, 39013-29-1; VI, 39013-30-4; VII, 39013-31-5; 3-(3,4-dimethoxyphenyl)propionic acid, 2107-70-2; 2-(3,4-dimethoxyphenyl)ethylamine, 120-20-7.

(7) G. Scheuing and B. Walach, German Patent 576,532 (1933); *Chem. Abstr.*, **27**, 5896 (1933).

Organocopper Chemistry. Reactions of Lithium Dialkylcopper Reagents with Activated Vinylcyclopropanes. An Instance of 1,7 Addition

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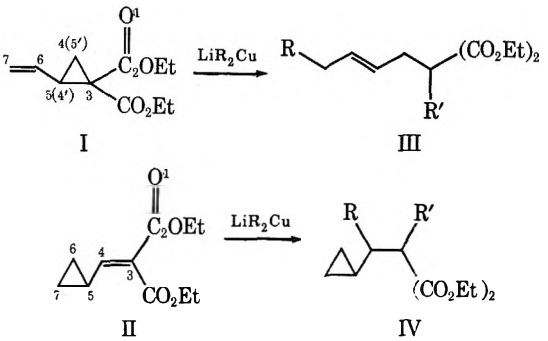
Alkylation of a wide variety of organic substrates using alkylcopper(I) "ate" complexes continues to be a subject of active interest.[1] The recently reported capabilities of organocopper species to perform 1,5 and 1,6 additions[2] (ω alkylation) prompts us to report our results concerning the reaction of I and II with lithium



dimethylcopper ($LiMe_2Cu$) and lithium di-*n*-butylcopper ($LiBu_2Cu$). In addition we report further observations which allow for simultaneous ω (1,7 or 1,4)[3a] and α-alkylation *via* addition of an alkylcopper "ate" complex to either I or II followed by alkylation[3b] of the resultant malonate anion.

In principle, compounds I and II possess multiple electrophilic sites. In addition to the trivial possibility of 1,2 addition, compound II might be attacked by nucleophiles in a 1,4 or 1,7 sense. Likewise, compound I might suffer nucleophilic attack in a 1,5, 1,5′, or 1,7 sense.[4] Our studies demonstrate, in each case, remarkable specificity toward olefin attack.

Treatment of I[5] with $LiMe_2Cu$ (1.25 equiv) in ether at 0° for 1 hr afforded an 87% yield of IIIa (R = CH_3; R′ = H). Its structure is assigned on the basis of the following data: ir max ($CHCl_3$) 5.80, 10.30 μ; nmr (CCl_4) δ 5.45 (m, 2 H, olefinic protons), 3.24 [t, 1 H, C**H**$(CO_2Et)_2$], 0.98 (t, 3 H, CH_2CH_3); *m/e* 228. This reaction constitutes a preferential and unambiguous 1,7 addition.[6-9] Similarly, $LiBu_2Cu$ underwent almost exclusive 1,7 addition in high yield (Table I).

In sharp contrast, treatment of II[10] with $LiMe_2Cu$ under similar conditions gave IVa (R = CH_3; R′ = H) in 92% isolated yield. The structure is assigned on the basis of the following data: ir max ($CHCl_3$) 5.80 μ; nmr (CCl_4) δ 3.25 [d, 1 H, C**H**$(CO_2Et)_2$], 1.08 (d, 3 H, $CHCH_3$), 0.80–0.05 (m, 5 H, cyclopropyl moiety);

(1) G. M. Whitesides, W. F. Fischer, Jr., J. SanFilippo, Jr., R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, **91**, 4871 (1968); E. J. Corey and G. H. Posner, *ibid.*, **89**, 3911 (1967), and **90**, 5615 (1968), and references cited therein.

(2) (a) E. J. Corey and P. L. Fuchs, *J. Amer. Chem. Soc.*, **94**, 4014 (1972); E. J. Corey, C. U. Kim, R. H. K. Chen, and M. Takeda, *ibid.*, **94**, 4395 (1972); G. Daviaud and P. Miginiac, *Tetrahedron Lett.*, 997 (1972). (b) For previous precedent in SN2′-type displacements using $LiMe_2Cu$, see R. J. Anderson, C. A. Henrick, and J. B. Siddall, *J. Amer. Chem. Soc.*, **92**, 735 (1970); E. E. van Tamlen and J. P. McCormick, *ibid.*, **92**, 737 (1970); R. J. Anderson, *ibid.*, **92**, 4978 (1970); R. W. Herr and C. R. Johnson, *ibid.*, **92**, 4979 (1970).

(3) (a) For a recent review of organocopper 1,4-addition reactions, see G. H. Posner, *Org. React.*, **19**, 1 (1972). (b) For alkylation of an enolate anion generated by addition of an organometallic reagent to an α,β-unsaturated ketone, see G. Stork, *Pure Appl. Chem.*, **17**, 383 (1968).

(4) We suggest the terms 1,5 and 1,5′ (which arises from alternative numbering) to signify alternate modes of homoconjugate addition and 1,7 to signify vinylogous homoconjugate addition. The terms 1,4 and 1,6 are thus reserved for classical Michael reactions.

(5) R. W. Kierstead, R. P. Linstead, and B. C. L. Weedon, *J. Chem. Soc.*, 3610 (1952).

(6) The normal mode of addition of nucleophiles to I is in the 1,5 sense.[7,8] The two serious exceptions to this rule are 1,7-mercaptan addition[7] and 1,7-enamine addition.[8] The former case is most probably the result of a free radical pathway.[9] The latter case may well be the result of 1,5-alkylation at nitrogen followed by Claisen rearrangement.

(7) J. M. Stewart and G. K. Pagenkopf, *J. Org. Chem.*, **34**, 7 (1969).

(8) S. Danishefsky, G. Rovnyak, and R. Cavanaugh, *Chem. Commun.*, 636 (1969).

(9) S. Danishefsky and R. Rovnyak, *J. Chem. Soc., Chem. Commun.*, 820 (1972).

(10) Prepared from the Knoevenagel condensation of diethyl malonate with cyclopropanecarboxaldehyde (see G. Rovnyak, Ph.D. Thesis, University of Pittsburgh, 1970).

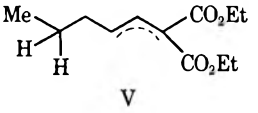
TABLE I
REACTIONS OF I WITH LiR_2Cu FOLLOWED BY R'X

$$I \xrightarrow[2.\ R'X]{1.\ LiR_2Cu} III$$

LiR_2Cu	R'X	Product[a]	Isolated yield, %
$LiMe_2Cu$		IIIa (R = CH_3; R' = H)	87
$LiMe_2Cu$	CH_3I	IIIb (R = R' = CH_3)	70
$LiMe_2Cu$	Allyl bromide	IIIc (R = CH_3; R' = allyl)	75
$LiMe_2Cu$	$C_6H_5CH_2Cl$	IIId (R = CH_3; R' = $CH_2C_6H_5$)	88
$LiBu_2Cu$		IIIe (R = C_4H_9; R' = H)	90
$LiBu_2Cu$	CH_3I	IIIf (R = C_4H_9; R' = CH_3)	75
$LiBu_2Cu$	Allyl bromide	IIIg (R = C_4H_9; R' = allyl)	88

[a] All substances gave nmr, ir, and analytical data in agreement with the indicated structures.

m/e 228. It is important to note that, under these conditions, we were unable to detect the formation of compound V which would have resulted from 1,7



V

addition to II. This result is of particular interest in connection with two recent findings. Marshall reported[11] competitive 1,4 and 1,7 addition of $LiMe_2Cu$ to a vinylogous cyclopropyl ketone in a decalin system. Stewart,[12] on the other hand, reported exclusive (albeit in low yield) 1,7 addition of mercaptans to a substrate more closely related to II. The case at hand seems to indicate a very pronounced preference for 1,4 addition in the absence of compelling steric factors.

ω-Alkylation (1,7 or 1,4) employing $LiMe_2Cu$ or $LiBu_2Cu$ with either I or II results in the formation of a stabilized anion which should be capable of undergoing alkylation. We have examined this possibility and report that one can effectively alkylate such anions with several halides (see Tables I and II).

TABLE II
REACTIONS OF II WITH LiR_2Cu, FOLLOWED BY R'X

$$II \xrightarrow[2.\ R'X]{1.\ LiR_2Cu} IV$$

LiR_2Cu	R'X	Product[a]	Isolated yield, %
$LiMe_2Cu$		IVa (R = CH_3; R' = H)	92
$LiMe_2Cu$	CH_3I	IVb (R = R' = CH_3)	93
$LiMe_2Cu$	Allyl bromide	IVc (R = CH_3; R' = allyl)	95
$LiBu_2Cu$	CH_3I	IVd (R = C_4H_9; R' = CH_3)	99
$LiBu_2Cu$	Allyl bromide	IVe (R = C_4H_9; R' = allyl)	98

[a] All substances gave nmr, ir, and analytical data in agreement with the indicated structures.

The conjugate 1,4- and vinylogous homoconjugate 1,7-addition processes involving organocopper species accompanied by α-alkylation illustrates a number of effective, specific operations which can be employed in organic synthesis.

Experimental Section[13]

Procedure for the Reaction of I or II with Lithium Dimethylcopper.—To a cooled (0°) stirred suspension of CuI (289 mg, 1.5 mmol) in 12 ml of anhydrous ether under an atmosphere of nitrogen was added 1.8 ml of 1.66 *M* ethereal methyllithium (3.0 mmol). To this colorless solution was added 212 mg of vinylcyclopropane I. After 1 hr at 0°, the reaction mixture was quenched by pouring it into a solution of ammonium chloride. Isolation with ether followed by short-path distillation [bp 80° (bath temperature) at 0.1 mm] afforded 198 mg (87%) of 1,7-addition product IIIa: ir max ($CHCl_3$) 5.80, 10.30 μ; nmr (CCl_4) δ 5.45 (m, 2 H, olefinic protons), 4.15 (q, *J* = 7 Hz, 4 H), 3.24 [t, 1 H, $CH(CO_2Et)_2$], 2.53 (m, 2 H), 1.28 (t, *J* = 7 Hz, 6 H), 0.98 (t, 3 H, CH_2CH_3); *m/e* 228.1362.

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 62.97; H, 8.77.

Procedure for the Reaction of I or II with Lithium Di-*n*-butylcopper.—To a cooled (−20°) stirred suspension of CuI (240 mg, 1.25 mmol) in 12.5 ml of anhydrous ether under an atmosphere of nitrogen was added 1.0 ml (2.5 mmol) of 2.5 *M* *n*-BuLi in hexane. After 30 min at −20°, vinylcyclopropane I (214 mg, 1.0 mmol) in 2.0 ml of ether was added dropwise and stirring at −20° was continued for 3 hr. The reaction mixture was quenched by pouring it into a solution of ammonium chloride. Isolation with ether and short-path distillation [bp 90° (bath temperature) at 0.1 mm] afforded 243 mg (90%) of 1,7-addition product IIIe: ir max (film) 5.80, 10.32 μ; nmr (CCl_4) δ 5.38 (m, 2 H, CH=CH), 4.14 (q, *J* = 7 Hz, 4 H), 3.24 [t, 1 H, $CH(CO_2Et)_2$], 2.50 (m, 2 H), 1.95 (m, 2 H), 1.25 (t, *J* = 7 Hz, 6 H), 0.88 (t, 3 H); *m/e* 270.

Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69. Found: C, 66.40; H, 9.62.

General Procedure for the Reaction of I or II with Lithium Di-*n*-butylcopper Followed by Treatment with R'X.—To a suspension of CuI (241 mg, 1.25 mmol) in 12.5 ml of anhydrous ether cooled to −20° under an atmosphere of nitrogen was added 1.0 ml (2.5 mmol) of *n*-BuLi (2.55 *M* in hexane) followed by the dropwise addition of 212 mg (1.0 mmol) of vinylcyclopropane II in 2.0 ml of ether. After 2 hr at −20°, the reaction mixture was warmed to room temperature and excess methyl iodide was added. The reaction mixture was stirred overnight at room temperature (18 hr) and was quenched by pouring it into an ammonium chloride solution. Isolation with ether followed by short-path distillation [bp 94° (bath temperature) at 0.15 mm] afforded 280 mg (99%) of ω (1,4), α dialkylated product IVd: ir max ($CHCl_3$) 5.81 μ; nmr (CCl_4) δ 4.11 (q, *J* = 7 Hz, 4 H), 1.35 (s, 3 H), 1.23 (t, *J* = 7 Hz, 6 H), 0.88 (t, 3 H), 0.70-0.05 (cyclopropyl moiety, 5 H); *m/e* 284.

Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.80; H, 9.77.

General Procedure for the Reaction of I and II with Lithium Dimethylcopper Followed by Treatment with R'X.—To a suspension of CuI (240 mg, 1.25 mmol) in 12.5 ml of anhydrous ether at 0° under an atmosphere of nitrogen was added 1.5 ml (2.5 mmol) of 1.66 *M* ethereal methyllithium followed by 214 mg (1.0 mmol) of vinylcyclopropane I in 2.0 ml of ether. After 1 hr at 0°, the reaction mixture was treated with excess benzyl chloride, warmed to room temperature, and allowed to stir overnight (18 hr). Usual work-up afforded after short-path distillation [bp 127° (bath temperature) at 0.13 mm] 278 mg (88%) of ω (1,7), α dialkylated product IIId: ir max (film) 5.79, 10.38 μ; nmr (CCl_4) δ 7.12 (s, 5 H), 5.42 (m, 2 H), 4.09 (q, *J* = 7 Hz, 4 H), 3.16 (s, 2 H), 2.43 (d, 2 H), 2.02 (m, 2 H), 1.19 (t, *J* = 7 Hz, 6 H), 0.98 (t, 3 H); *m/e* 318.

Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.45; H, 8.29.

Registry No.—I, 7686-78-4; II, 39000-53-8; IIIa, 36276-65-0; IIId, 39000-72-1; IIIe, 36276-67-2; IVa, 39013-57-5; IVd, 39013-58-6; $LiMe_2Cu$, 15681-48-8; $LiBu_2Cu$, 24406-16-4; CH_3I, 74-88-4; allyl bromide, 106-95-6; $C_6H_5CH_2Cl$, 100-44-7.

Acknowledgments.—We thank Professor S. Danishefsky for many stimulating discussions and Mr. P. Cain for the preparation of compound I. Acknowledgment is to the Science Development Program of the National Science Foundation (GU 3184) for support of this research.

(11) J. A. Marshall and R. A. Ruden, *J. Org. Chem.*, **37**, 659 (1972).

(12) J. M. Stewart and B. R. Olsen, *J. Org. Chem.*, **33**, 4534 (1968).

(13) Nmr measurements were carried out on a Varian A-60D spectrometer using TMS as an internal reference. A Perkin-Elmer Model 247 was used for ir studies. Mass spectral data were obtained on an LKB-9 spectrometer. Elemental analyses were determined by Galbraith Laboratories, Knoxville, Tenn. Anhydrous cuprous iodide was purchased from Alpha Inorganics, Inc., and was sufficiently dry and pure for direct use.

4-(2-Thienyl)-5-methylpyrimidine. An Anomalous Leuckart Product

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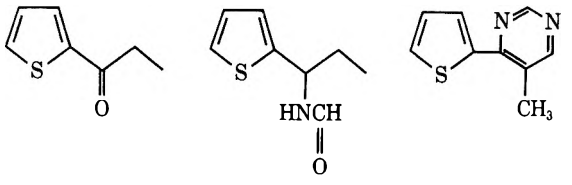
Received February 7, 1973

The Leuckart reaction is a well-known procedure for the direct conversion of aldehydes and ketones to primary amines upon heating with formic acid or certain of its derivatives.[1] When this reaction is carried out using 2-propionylthiophene (1) and formamide, one obtains in addition to the expected 1-(2-thienyl)-1-aminopropane,[2,3] a minor product I, mp 74–76°, previously[2] assigned the *N*-formyl structure 2. The correct structure of I has now been determined to be the thienyl-substituted pyrimidine 3.



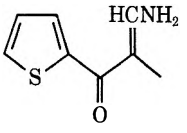
1 2 3

N-Formyl derivatives are frequently obtained as by-products in the Leuckart reaction,[4] but the formation of pyrimidines in this reaction has not previously been reported. Authentic 2, bp 121–122° (0.6 mm), has now also been prepared.

Doubts concerning the assigned structure of I were raised by the absence of a carbonyl absorption in the ir spectrum. The mass spectrum of I indicated a molecular ion of 176 rather than the expected peak of 169 and a parent M − 1 peak of 175 with little further significant fragmentation. These data, coupled with the elemental analysis, gave a molecular formula of $C_9H_8N_2S$. The nmr spectrum showed two low-field singlets at δ 9.03 and 8.58, a complex aromatic resonance centered at 7.38 due to the thienyl protons, and an aromatic methyl singlet at 2.53 in a ratio of 1:1:3:3. The low-field singlets are characteristic of pyrimidine resonances and the chemical shifts (see Experimental Section) are virtually identical with those found for 5-methylpyrimidine.[5a] Further, the aromatic portion of the nmr spectrum is qualitatively similar to the published spectrum of 4-(2-thienyl)-5-bromopyrimidine.[6] These data are consistent only with structure 3.

4-(2-Thienyl)-5-methylpyrimidine (3) has not previously been reported; however, certain analogs have been synthesized by the acid-catalyzed condensation of formamide with 2-thienyl ethynyl ketone[7] or by the addition of 2-thienyllithium across the azomethine bond of the appropriate pyrimidine followed by oxidation.[6,8] Other pyrimidines have been prepared by the reaction of formamide with aromatic ketones possessing an active methylene group, but only in the presence of strong acids.[5a,9]

The formation of pyrimidine 3 during the Leuckart reaction may proceed *via* intermediate 4, formed as a result of condensation catalyzed by small amounts of formic acid that may be liberated during the reaction, followed by further condensation of 4 with formamide.[10]



4

This suggests that pyrimidines may also have been formed as by-products in other Leuckart reactions but, being very much higher boiling, have been discarded with the distillation residues and hence have not been previously observed.

Experimental Section[12]

1-(2-Thienyl)-1-aminopropane and 4-(2-Thienyl)-5-methylpyrimidine (3).—A mixture of 56 g (0.4 mol) of 2-propionylthiophene (Columbia Organic Chemical Co.) and 72 g (1.6 mol) of formamide was heated at 180–190° under N_2 for 24 hr. Ammonium carbonate (13.2 g) sublimed into the condenser and was periodically removed. The reaction mixture was cooled to room temperature, 200 ml of 30% sodium hydroxide solution was added, and the mixture was again heated at reflux. After 10 hr the mixture was cooled and extracted with ether and the combined ether extracts were washed with water and then 50% hydrochloric acid. The acidic solution was rendered alkaline with aqueous sodium hydroxide and extracted with ether and the combined ether extracts were dried ($MgSO_4$). After removal of the solvent, the residual oil (48.3 g) was fractionated to give 35.4 g (63%) of 1-(2-thienyl)-1-aminopropane: bp 45–48° (1.2 mm); $n^{25}D$ 1.5330 [lit.[2] bp 89–91° (13 mm)]; nmr ($CDCl_3$) δ (TMS) 7.08 (m, 3, ArH), 4.10 (t, 1, methine), 1.75 (m, 2, J = 7.5, 6.8 Hz, $-CH_2-$), and 0.91 (t, 3, J = 7.5 Hz, $-CH_3$).

Further fractionation gave 7.4 g (11%) of 4-(2-thienyl)-5-methylpyrimidine (3): bp 104–105° (1.2 mm); mp 74–76° (needles from ethanol) [lit.[2] (erroneously assigned structure 2) bp 174–178° (12 mm), mp 75–76°]; nmr ($CDCl_3$) δ (TMS) 9.03 (s, 1, pyrimidine H_2), 8.58 (s, 1, pyrimidine H_4), 7.83–7.08 (m, 3, thiophene H), and 2.53 ppm (s, 3, $-CH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 178 (5), 177 (15), 176 (98), 175 (100), 148 (8), 131 (8), 121 (9).

Anal. Calcd for $C_9H_8N_2S$: C, 61.34; H, 4.58; N, 15.89. Found: C, 61.34; H, 4.61; N, 15.78.

Compound 3 readily forms salts: hydrochloride, mp 237–239° (from ethanol) (lit.[2] mp 234–235°); picrate, mp 195–197° (from ethanol).

***N*-[1-(2-Thienyl)]propylformamide (2).**—A mixture of 2.00 g (14.1 mmol) of 1-(2-thienyl)-1-aminopropane and 1.82 g (16

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(9) H. Bredereck, R. Gompper, H. Schuh, and G. Theilig, "Newer Methods of Preparative Organic Chemistry," Vol. 3, W. Foerst, Ed., Academic Press, New York, N. Y., 1964, p 241.

(10) A number of mechanistic pathways are possible; however, on the basis of current ideas concerning the mechanism of the Leuckart reaction[11] this route seems to be the most likely.

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(12) Melting and boiling points are uncorrected. Nuclear magnetic resonance (nmr) spectra were recorded on a Jeolco C60H model spectrometer and mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. We wish to thank Miss M. Carroll, Dr. E. White, and Mr. R. Warren and coworkers of the Analytical and Physical Chemistry Section, Smith Kline & French Laboratories, for the elemental analyses, mass spectra, and nmr spectra.

mmol) of ethyl formate was refluxed for 12 hr. All volatiles were removed at reduced pressure, the residual oil was dissolved in methylene chloride, washed with dilute hydrochloric acid, then water, and the organic phase was dried ($MgSO_4$). The solvent was removed and the residual oil was distilled, giving 1.39 g (58%) of formamide **2**: bp 121–122° (0.6 mm); $n^{25}D$ 1.5433; ir (neat) 1675 (amide C=O) and 3290 cm^{-1} (amide NH); nmr ($CDCl_3$) δ (TMS) 8.15 (s, 1, HCON), 7.13 (m, 3, ArH), 6.75 (m, 1, NH), 5.23 (m, 1, J = 16.5, 7.5 Hz, CH), 1.87 (m, 2, J = 7.5 Hz, $-CH_2-$), and 0.93 ppm (t, 3, J = 7.5 Hz, $-CH_3$); mass spectrum (70 eV) m/e (rel intensity) 169 (30), 140 (100), 113 (36), 97 (7), 85 (25).

Anal. Calcd for $C_8H_{11}NOS$: C, 56.77; H, 6.55; N, 8.28. Found: C, 56.60; H, 6.43; N, 8.44.

Addition of deuterium oxide and a trace of trifluoroacetic acid to the nmr solution ($CDCl_3$) resulted in the complete loss of the peak at δ 6.75 due to the amide proton and the collapse of the methine AB quartet at δ 5.23 to a triplet, J = 7.5 Hz.

Registry No.—**1**, 13679-75-9; **2**, 39207-57-4; **3**, 39204-58-5; **3** picrate, 39204-59-6; 1-(2-thienyl)-1-aminopropane, 6315-55-5; formamide, 75-12-7; ethyl formate, 109-94-4.

Preparation and Purification of Tetrasodium *meso*-Tetra(*p*-sulfophenyl)porphine. An Easy Procedure[1]

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Tetraphenylporphine sulfonate was first reported by Winkelman, who studied localization of this compound in tumors. He found that it could be localized with a higher concentration ratio in animal tumors than in other tissues.[3,4] It was later found that Winkelman's sample is, in fact, a mixture of various isomers.[5] The sodium salt of *meso*-tetra(*o*-sulfophenyl)porphine was recently prepared in low yield by condensing pyrrole and benzaldehyde sulfonic acid (sodium salt) in *n*- or *tert*-butyl alcohol in the presence of sodium acetate.[6] *meso*-Tetra(*p*-sulfophenyl)porphine was prepared by heating *meso*-tetraphenylporphine and concentrated sulfuric acid on a steam bath for 4 hr. The diacid was precipitated by adding the requisite amount of water. The tetraammonium salt was precipitated by dissolving the diacid in methanolic ammonia and then adding acetone. Further purification of the tetraammonium salt was carried out by a cumbersome procedure involving six successive reprecipitations from a methanolic solution with acetone. The tetraammonium salt of *meso*-tetra(*p*-sulfophenyl)-porphine was further converted to the tetrasodium salt by treating the former with sodium methoxide.[4] We wish to report an easy preparation and purification procedure for the tetrasodium *meso*-tetra(*p*-sulfophenyl)porphine (60% yield).

(1) Unusual Metalloporphyrins. XVI.
(2) To whom correspondence should be addressed.
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Experimental Section

Finely powdered *meso*-tetraphenylporphine (2 g)[7] was mixed with 50 ml of concentrated sulfuric acid. The mixture was heated on a steam bath for 4–5 hr. After cooling to room temperature, the solution was filtered through a sintered glass frit and the filtrate was diluted carefully to 1. The dilute solution was heated and a sludge of lime was added slowly with stirring until the solution changed to a permanent purple color. Calcium sulfate was filtered off and washed with a minimum quantity of hot water, which was then combined with the filtrate. Crushed Dry Ice was added to the filtrate and was filtered. The filtrate was concentrated to a small volume (about 100 ml) and the pH of the final warm solution was regulated at 8–10 by adding the required quantity of concentrated sodium carbonate solution. Calcium carbonate was removed by filtration and washed with water, which was then combined with the filtrate. Hot ethanol (90%) in small quantities was periodically added to the filtrate, which was further concentrated on a steam bath. The saturated solution was cooled at room temperature and crystals of tetrasodium *meso*-tetra(*p*-sulfophenyl)porphine (I) were obtained. They were filtered off and washed with a minimum quantity of cold 90% ethanol. Finally the material was dried at 100° for 1 hr. The water content in compound I was determined by heating it under vacuum at 140° for 15 hr. I has an empirical formula of $C_{44}H_{50}N_4O_{24}S_4Na_4$ with 12 water molecules. *Anal.*[8] Calcd for $C_{44}H_{26}N_4O_{12}S_4Na_4 \cdot 12H_2O$: N, 4.50; S, 10.29. Found: N, 4.54; S, 10.55. The compound is very soluble in water. The visible spectrum of I (H_2O) shows five peaks at 413 (soret), 506 (I), 543 (II), 570 (III), and 634 (IV) nm (rel intensity I > II > III > IV). The ir spectrum of I (KBr) shows four strong bands at 1226, 1194, 1134, and 1046 cm^{-1} due to sulfonic acid (salt) absorption[9] in addition to free porphyrin vibrations. The ^1H nmr (T-60 Varian Associates) of I (D_2O) shows pyrrole protons at δ 7.51 and two doublets due to protons of phenyl groups centered at δ 6.85 and 7.85 with a coupling constant of 8 Hz.[4] The ratio of peak areas of pyrrole protons and phenyl protons is 1:2. This excludes the possibility of substitution of the pyrrole protons and supports the substitution of the phenyl protons by four sulfonate groups. Furthermore, the presence of the two doublets at δ 6.85 and 7.85 in the ^1H nmr of I shows clearly that four sulfonate groups are substituted only at para positions of the phenyl groups.

Registry No.—Tetrasodium *meso*-tetra(*p*-sulfophenyl)porphine, 39050-26-5; *meso*-tetraphenylporphine, 917-23-7.

Acknowledgment.—This work was supported by NSF (Grant No. GP-28685). We thank Dr. James Francis for valuable discussions.

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The Rearrangement of α-Ethynyl Alcohols to Unsaturated Carbonyl Compounds (The Rupe Reaction)

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The identity of the products from, and the mechanism of, the Rupe reaction has been debated in the

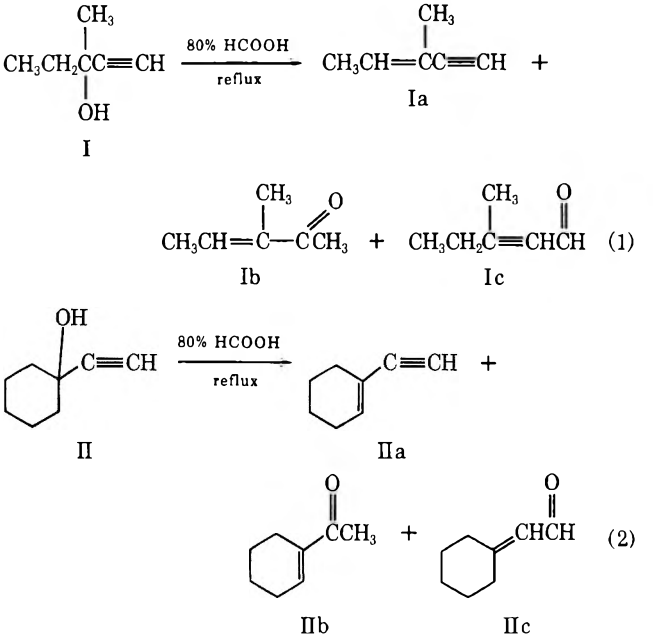
(1) Abstracted in part from the M.S. thesis of A. D. Anderson, Central Washington State College, Aug 1967. The Research Corporation provided funds that allowed Miss Anderson's work.

literature since Hans Rupe first reported that α-ethynyl carbinols can be rearranged to carbonyl products when refluxed with formic acid.[2] Rupe believed that the carbonyl products were α,β-unsaturated aldehydes. More recent authors have reported that the major carbonyl products were α,β-unsaturated ketones.[3] Some authors report formation of both aldehydes and ketones, while others report only ketones.[4,5] Several others report formation of hydrocarbon products the structures of which have been determined to be vinylacetylenes.[6,7] Surprisingly, several authors have proposed mechanisms for the reaction despite the fact that consistent agreement as to the structures and relative proportions of products has never been reached and that few other mechanistic studies have been performed.[8-10] The work described in this paper was prompted by a need to understand the reason for the discrepancies and an interest in gaining other mechanistic data.

Results and Discussion

Two typical α-ethynylcarbinols were chosen for study. The carbinols were 3-methyl-1-pentyn-3-ol (I) and 1-ethynyl-1-cyclohexanol (II). Each of the carbinols was subjected to normal Rupe reaction conditions.[2] Normal conditions involve refluxing the carbinols with an excess of formic acid for periods of from 2 to 8 hr. In the studies reported in the literature to date, the organic products have been isolated by classical work-up and identification procedures. These have involved isolation of the organic products by organic solvent extraction and distillation followed by preparation of various derivatives and/or formation of other organic compounds. In our study the organic products were separated from the reaction mixture by organic solvent extraction and then each major organic product was detected and isolated by gas–liquid partition chromatography (glpc). The structure of each isolated product was then determined by use of ir, uv, and nmr and by use of classical techniques.

Carbinols I and II produce several organic products, but in each case three of the products accounted for greater than 85% of the total initially formed organic material. In our study, as has been established before, some of the initially formed products undergo subsequent acid-catalyzed polymerization to compounds of not much interest.[8] Consequently, the yield of initially formed products normally varies from 40 to 70% depending on the structure of the starting carbinol. Over the years interest has focused on only three of the several organic products of the reaction, and these we have found to constitute at least 85% of the initially formed products of reaction of carbinols I and II. Equations 1 and 2 show the



primary reactions that were found to take place and that will be discussed further.

Table I presents a list of the relative percentages

TABLE I

Compd	Reaction time, hr (approx)	Reaction temp, °C	% vinylacetylene	% ketone	% aldehyde
I	2	85–90	20	60	13
II	2	85–90	2	63	4

of the primary products of interest and carbinol reactant following a normal Rupe reaction.

During the study to obtain the data in Table I it was found that the relative percentage of aldehyde formed in the reaction was higher if product analysis was done early in the course of the reaction. As a consequence, experiments were carried out allowing a time-dependent product analysis. In this study it was found that, when a 10:1 ratio of acid to carbinol was employed at reflux temperatures, the reaction rate was too fast to allow analysis. As a result, a modified procedure was adopted. The modification involved treating the carbinol with formic acid at a 1:5 ratio at reflux temperatures rather than a 1:10 ratio. This modification produced nearly identical product distribution, but at a slower reaction rate.

A time-dependent product analysis study was then carried out using a 5:1 ratio of formic acid to carbinol at reflux and several other temperatures. Table II is a summary of the relative percentages of the principal organic products that were determined at several times in the course of the reaction at two different temperatures.

The results of the experiments described in this paper suggest that the reason for the past controversy over the nature and distribution of carbonyl products formed in the Rupe reaction was due to lack of control of experimental conditions, as has been implied by Parham.[9] As noted earlier in this paper, early workers apparently simply mixed reagents, brought

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TABLE II

Compd	Reaction time, hr	Reaction temp, °C	% reaction[a]	% vinylacetylene	% ketone	% aldehyde
I	1	85–90	60	26	51	16
	2	85–90	66	21	60	13
	4	85–90	76	19	70	7
	8	85–90	88	13	83	5
	0.25	55–60	17	5	1	91
	1	55–60	20	7	2	90
	4.5	55–60	25	25	3	72
II	1	85–90	51	4	83	13
	2	85–90	84	2	93	4
	4	85–90	89	2	95	2
	8	85–90	95	1	96	1
	0.25	60–70	14	17	9	75
	1.5	60–70	27	40	14	47

[a] Per cent reaction based on per cent unreacted alcohol.

the reaction mixture to reflux temperatures, and heated it for indefinite periods of time. Product identity, isolation, and composition was done using classical techniques, which probably has produced some of the uncertainty in the distribution of the carbonyl products produced. As a consequence, the mechanisms based on product analysis that have been proposed for the Rupe reaction are subject to question. Some other mechanistic studies have, however, been reported. Ansell, for example, has shown that the vinylacetylenes produced in the reaction undergo an acid-catalyzed hydration reaction, but at rates much slower than ketone formation.[8] We have found this to also be the case in our study. Vinylacetylenes Ia and Ib were found to undergo no hydration reaction under the conditions of this study. This work obviates several reports that the vinylacetylenes are required intermediates, although minor amounts of ketone may have been formed by this reaction in other reported work. In the same report, Ansell also verified that the α,β-unsaturated aldehydes undergo self-condensation reactions and that the vinylacetylenes undergo oxidation reactions. We found this to also be the case in our study. When mixtures of the three principal organic products were subjected to Rupe conditions, there were no changes in the relative proportions of the starting materials. However, considerable polymeric products were formed.

The numerous competing side reactions of the products produced, therefore, greatly complicate a detailed kinetic study and are no doubt the cause of production of substantial amounts of the colored, high molecular weight organic products that always accompany the reaction. Work has been initiated in our laboratory to develop appropriate Lewis acid catalysts which we have found produce the same principal organic products but apparently do not result in the numerous side reactions of the principal organic products. Thus, we hope in the near future to report a detailed kinetic study and also the results of appropriate labeling studies.

Experimental Section

Materials and Equipment.—The starting carbinols, 3-methyl-1-pentyn-3-ol (I) and 1-ethynyl-1-cyclohexanol (II), were prepared according to a modified method of Campbell, Campbell, and Eby.[11] Metallic sodium (11.5 g) was added slowly and with constant stirring to 500 ml of liquid ammonia which was being perfused with acetylene. Following sodium addition either 31 g of 2-butanone or 49 g of cyclohexanone was slowly added through a dropping funnel. The solvent, liquid ammonia, was allowed to evaporate and the resulting solid was hydrolyzed with water. The organic material was extracted with ether, washed, dried, and purified by vacuum distillation. This procedure afforded 30 g (61%) of carbinol I: bp 77–80° (150 mm); 99% pure by glpc, R_v 312 ml; nmr (neat) δ_{TMS} 2.5 (s, 1, OH), 2.4 (s, 1, C≡CH), 1.1 (t, 3, CH_2CH_3, J = 7 Hz), 1.6 (m, 5, CCH_3, CH_2CH_3); ir (neat) 3.2 (OH), 6.8, 7.3, 7.5, 7.7, 7.8, 8.5, 8.8, 9.6, 10.0, 10.8 μ (OH). It also gave 25 g (40%) of II: bp 76–78° (17 mm); 99% pure by glpc, R_v 345 ml; nmr (CCl_4) δ_{TMS} 3.2 (s, 1, OH), 2.5 (s, 1, C≡CH), 1.70 (m, 10, ring CH_2); ir (CCl_4) 2.9 (OH), 3.4 (CH), 6.9, 7.3, 7.8, 7.9, 8.9 (OH), 10.8 μ.

Spectra were recorded on a Perkin-Elmer 137B prism ir spectrophotometer, a Perkin-Elmer Hitachi 139 uv-visible spectrophotometer, and a Varian HA60IL nmr spectrometer. Gas–liquid partition chromatography was carried out with a Perkin-Elmer 811 equipped with a 10 ft × 0.125 in. aluminum column packed with a 20% silicone DC200 on 70/80 Anakrom. Operation conditions for carbinol I were injector, 200°; column, 110°; detector, 160°; He flow rate, 25 ml/min. For II they were injector, 200°; column, 130°; detector, 200°; He flow rate 25 ml/min. The glpc data was standardized by the internal normalization method that is applicable for hydrogen flame detectors.[12]

3-Methyl-3-penten-2-yne (Ia).—The vinylacetylene Ia detected as a product from treatment of carbinol I was prepared according to the method of Newman, *et al.*[13] Thionyl chloride (11.8 g) in dry ether (7.5 ml) was added dropwise with vigorous stirring to 9.8 g of carbinol I (dried over molecular sieves 5A) in 18 ml of dry pyridine (dried over BaO) in 20 ml of dry ether. The drop rate and heating were set to maintain gentle reflux. After refluxing for 5 hr, cold water was added and then cold, dilute HCl. The vinylacetylene Ia, 4 g (50% yield), was recovered by distillation: bp 70–72° (760 mm);[14] glpc R_v 45 ml; ir (neat) 3.05 (C≡CH), 3.4 (CH), 4.8 (C≡C), 6.1 (C=C), 7.0, 7.7, 11.0, 12.0, 16.0 μ.

1-Ethynyl-1-cyclohexene (IIa).—The vinylacetylene IIa detected as a product from formic acid treatment of carbinol II was prepared according to the method described above except that 12.4 g of starting carbinol was used. Following vacuum distillation 5.8 g (55% yield) of vinylacetylene IIa was recovered: bp 42–43° (13 mm);[15] glpc R_v 100 ml; ir (neat) 3.3 (C≡CH), 3.4 (CH), 4.75 (C≡C), 6.95 (C=C), 7.70, 11.0, 11.9, 12.0, 12.6, 15.8, 18.8, 19.3 μ.

3-Methyl-3-penten-2-one.—The α,β-unsaturated ketone Ib detected as a product from formic acid treatment of carbinol I was isolated and purified following a Rupe reaction. The physical and spectral properties of the compound were obtained and compared to those of authentic material obtained from Alpha Chemical Co. Ketone Ib was isolated and purified *via* glpc (99% pure, R_v 250 ml); bp 62–65° (50 mm); ir (neat) 3.3 (CH), 5.9 (C=O), 5.95 (C=C), 6.9, 7.0, 7.6, 8.5, 8.7, 9.2, 9.7, 10.4, 12.0, 13.9 μ; nmr (CCl_4) δ_{TMS} 6.65 (q, 1, =CH, J = 4 Hz), 2.18 (s, 3, CCH_3), 1.7 (m, 6, C=CH_3); λ_{max}^{EtOH} 228 nm (ϵ 12,800) [lit.[4] λ_{max}^{EtOH} 230 nm (ϵ 12,600)]; negative to Schiff reagent.

1-Acetyl-1-cyclohexane.—The α,β-unsaturated ketone IIb detected as a product from formic acid treatment of carbinol II was isolated and purified following a Rupe reaction. The physical and spectral properties of the compound were obtained and compared to those of authentic material obtained from Alpha Chemical Co. Ketone IIb was isolated and purified *via* glpc (99% pure, R_v 300 ml): bp 111–114° (50 mm); ir (neat) 3.3 (CH), 5.9 (C=O), 6.05 (C=C), 6.9, 7.2, 7.4, 7.8, 8.0, 8.08, 8.8, 9.2, 9.3, 10.2, 10.8, 11.0, 11.7, 11.8, 12.5 μ; nmr (CCl_4) δ_{TMS} 6.73 (m, 1, =CH), 2.12 (s, over m, 7), 1.69 (m, 4); λ_{max}^{EtOH} 232 nm (ϵ 14,000) [lit.[5] λ_{max}^{EtOH} 233 nm (ϵ 12,500)]; negative to Schiff reagent.

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3-Methyl-2-pentenal.—The α,β-unsaturated aldehyde Ic detected as a product from formic acid treatment of carbinol I was isolated and purified following a Rupe reaction. The physical and spectral properties of the compound were obtained and used to establish the structure of the aldehyde. Aldehyde Ic was isolated and purified *via* glpc (95% pure, R_v 300 ml): ir (neat) 3.4 (CH), 5.8 (C=O), 5.9 (C=C), 6.8, 7.2, 8.4, 8.6, 8.9, 9.4, 9.6, 9.8, 10.7, 11.5, 12.3 μ; nmr (CCl_4) δ_{TMS} 9.4 (m, 1), 6.8 (s, 5), 6.1 (m, 1), 2.1 (t, 3); positive to Schiff reagent instantaneously.

Cyclohexlideneacetaldehyde.—The cyclic α,β-unsaturated aldehyde IIc detected as a product from formic acid treatment of carbinol II was isolated and purified following a Rupe reaction. The physical and spectral properties of the compound were obtained and used to establish the structure of the aldehyde. Aldehyde IIc was isolated and purified *via* glpc (95% pure, R_v 450 ml): bp 114–117° (50 mm); λ_{max}^{EtOH} 235 nm (ϵ 14,500) [lit.[5] λ_{max}^{EtOH} 235 nm (ϵ 14,400)]; positive to Schiff reagent instantaneously.

Rupe Reaction Conditions.—A 1:5 or a 1:10 molar ratio of carbinol to 85% formic acid were mixed and heated at selected temperatures for each time period ranging from 15 min to 8 hr. The reaction mixture was cooled in an ice bath and neutralized with cold 5% sodium hydroxide until the organic layer was completely separated and the aqueous layer was washed twice with small portions of hexane. The combined organic fractions were combined, washed twice with small portions of water, and dried over anhydrous sodium sulfate. Aliquot portions of each reaction mixture were then subjected to glpc analysis.

Registry No.—I, 77-75-8; Ia, 1574-33-0; Ib, 565-62-8; Ic, 3592-19-6; II, 78-27-3; IIa, 931-49-7; IIb, 932-66-1; IIc, 1713-63-9; 2-butanone, 78-93-3; cyclohexanone, 108-94-1; acetylene, 74-86-2.

The [3,3]-Sigmatropic Rearrangement of Allylic Dialkylthiocarbamates

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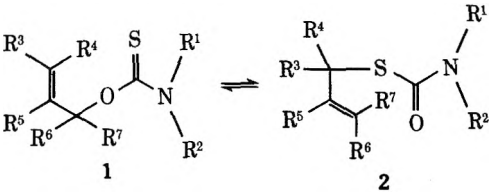
In the course of work on the synthesis of juvenile hormone analogs by way of [3,2]-sigmatropic rearrangements of sulfonium ylides,[1] a general route to hindered allylic thiols and sulfides was needed. It was clear from the work of Newman and Karnes[2] that the dialkylthiocarbamate linkage was more stable when joined through the sulfur than when joined through the oxygen. These workers reported[2] that O-aryl dialkylthiocarbamates could be converted to S-aryl dialkylthiocarbamates when heated at 130–335°, the temperature depending upon the ring substituents. It seemed that the added stability of the sulfur linkage could provide the driving force for a [3,3]-sigmatropic rearrangement when an O-allylic dialkylthiocarbamate was employed.

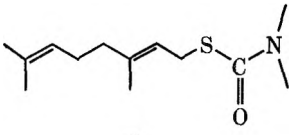
[3,3]-Sigmatropic rearrangements have been reviewed,[3] and more recent examples have been reported.[4,5] The same skeletal sequence of atoms as the thiocarbamates of this report has been observed with thionocarbonates,[6] and more recently with two allylic xanthates of a carbohydrate series.[7] Although both aryl[2] and alkyl[8] dialkylthiocarbamates have been pyrolyzed, allyl dialkylthiocarbamates are known primarily in the patent literature, and a limited amount of chemistry has been reported on them.

We wish to report the successful conversion of a series of O-allyl dialkylthiocarbamates to S-allyl dialkylthiocarbamates in which the allyl group is rearranged, as required by an electrocyclic mechanism. This transformation is illustrated by structures **1** and **2**, and Table I shows some of the compounds which



1 **2**

have been employed in this reaction. The temperature required for the reaction depends principally on the substituents on the allylic carbon to which the oxygen is originally attached. When this carbon is primary, the temperature required for 90% reaction in 20 min is 130–140°. The corresponding temperature for secondary carbamates is around 100–110°, while tertiary derivatives such as **1b**, **1l**, and **1m** cannot be isolated, but rearrange at room temperature or below to the S-allyl derivatives **2b**, **2l**, and **2m**. A competing reaction is noted if the temperature rise is not controlled adequately. For example, if **1a** is heated at greater than 150°, dissociation apparently occurs, as evidenced by the formation of **3** in small amounts.



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That the driving force for this rearrangement is strong is seen by the rearrangement of **1c**, in which conjugation of the double bond with the aromatic ring is destroyed. The rate of conversion of **1c** to **2c** is about the same as the rate for the unsubstituted **1e** to **2e**.

The rearrangements were monitored by ir, tlc, or nmr. The O-allyl derivatives showed strong bands at 1530 and 1190 cm^{-1}, and pyrolysis resulted in the diminishing of these bands and enhancement of the carbonyl band at about 1660 cm^{-1} for the S-allyl product. On silica gel tlc, the O-allyl derivative always had a higher rate of flow than the S-allyl derivative. Allyl isomerization produced changes in the nmr patterns, and protons α to oxygen and sulfur were in the predictable positions. In general, the dimethylamino group occurred as two peaks in the O-allyl compounds, but as a sharp singlet for the S-allyl isomers.

Hydrolysis of **2a** with sodium hydroxide in aqueous methanol did not give linalylthiol **5** as expected, but

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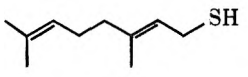
TABLE I[a]

ALLYLIC THIOCARBAMATES 1 AND 2

	R³	R⁴	R⁵	R⁶	R⁷
a	$(CH_3)_2C{=}CHCH_2CH_2$	CH_3	H	H	H
b	H	H	H	CH_3	$(CH_3)_2C{=}CHCH_2CH_2$
c	C_6H_5	H	H	H	H
d	CH_3	H	H	H	H
e	H	H	H	H	H
f	H	H	H	CH_3	H
g	H	H	CH_3	CH_3	H
h	H	H	H	$CH_3CH_2CH_2$	H
i	$CH_3CH_2CH_2$	H	H	H	H
j	$CH_3CH_2CH_2$	H	CH_3CH_2	H	H
k	H	$-(CH_2)_3-$ bridge R⁴ to R⁶	H	$-(CH_2)_3-$ bridge R⁴ to R⁶	H
l	H	H	H	CH_3	CH_3
m	H	H	H	C_6H_5	C_6H_5
n	CH_3	CH_3	H	CH_3	H

[a] $R^1 = R^2 = CH_3$ except for example j, where they form a piperidine ring, and example k, where $R^1 = R^2 = CH_3CH_2$.

instead yielded geranylthiol **4**. Partial hydrolysis showed no linalylthiol present at any time, but only **2a** and geranylthiol. We believe that this result reflects the instability of the hindered thiols in base in favor of the less hindered isomers. Reduction of **2a** with lithium aluminum hydride, however, did give the linalyl isomer **5**, which was isolated without the addition of acid or excess water. The thiocarbamate **2c** could also be reduced with lithium aluminum hydride to the thiol **6**, although, if the mixture was allowed to



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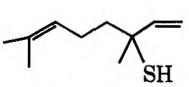

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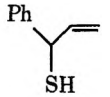

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stand overnight after the addition of water, the product was cinnamylthiol.

This thiocarbamate rearrangement thus provides a route to hindered allylic thiols which are otherwise relatively inaccessible. Displacement of hindered allylic halides or tosylates goes in SN2′ fashion,[9] yielding the less hindered thiols or sulfides. Hindered allylic thiols and even sulfides[1b] are unstable to acid, in which they rearrange to the less hindered isomers.

The linalylthiol obtained from the thiocarbamate has been used in the synthesis of 9-aryl-2,6-nonadienes, which are active[10] as mimics of some of the natural juvenile hormones.[11] The required intermediate sulfides **7** were made by treating the linalylthiol with benzylic halides. Generation of a sulfonium ylide **8** was accomplished using benzyne made from 2-fluorophenylmagnesium bromide. These ylides are not isolable, but undergo the [3,2]-sigmatropic rearrangement previously described[1] to give the sulfide **9**. This sulfide is then reduced with Raney nickel to give the juvenile hormone analog **10**. Thus, the availability of hindered thiols by way of the thiocarbamate rearrangement has made possible the synthesis of biologically active compounds from a previously known ylide rearrangement.

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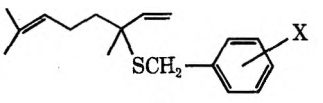

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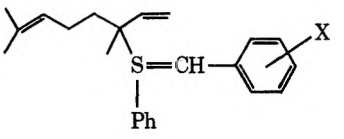

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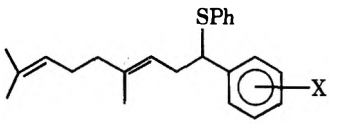

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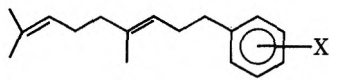

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Experimental Section

Nmr spectra were measured on a Varian A-60A instrument in $CDCl_3$. Chemical shifts are reported in parts per million from internal TMS, and are followed by parentheses giving multiplicity of signal, coupling constant if applicable, and number of protons. Spin multiplicity is given by s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. All compounds designated by an asterisk after the name showed satisfactory analytical data (±0.3% for C, H, N, and S). Silica gel for chromatographic separations was Davison Chemical grade 62 (60–200 mesh). Diethylthiocarbamoyl chloride was a gift of the Pennsalt Chemicals Corp.

Preparation of O-Allyl Dialkylthiocarbamates.—The O-allyl derivatives were prepared by the published procedure[2] for the corresponding O-aryl compounds, and one example illustrates the process. Sodium hydride (4.8 g, 57% in mineral oil) was washed with absolute ether before 40 ml of DMF was added. Geraniol (15.4 g, 0.1 mol) in DMF (40 ml) was added in portions and the mixture was stirred under nitrogen for 1 hr. The mixture was cooled to 0°, and 12.4 g (0.1 mol) of dimethylthiocarbamoyl chloride was added in DMF (30 ml). The ice bath was removed and the mixture was heated to 60° over 1 hr before cooling and pouring into 1% KOH (400 ml). The aqueous layer was saturated with NaCl and extracted with two 200-ml portions of benzene–hexane. The combined extracts were washed with 100 ml of saturated NaCl and then dried over $MgSO_4$ before the solvents were removed under vacuum. Chromatography over silica gel in benzene–hexane gave a clear oil (17 g), identified as *O*-geranyl dimethylthiocarbamate* (**1a**): nmr δ 5.42 (broad t, J = 7 Hz,

1), 5.05 (m, 1), 4.96 (d, J = 7 Hz, 2), 3.35 (s, 3), 3.10 (s, 3), 2.08 (m, 4), and 1.66 (m, 9).

O-Cinnamyl dimethylthiocarbamate* (**1c**) was obtained as a clear oil: nmr δ 7.30 (m, 5), 6.71 (d, J = 16 Hz, 1), 6.83 (two triplets, J_1 = 16, J_2 = 5 Hz, 1), 5.13 (d, J = 5 Hz, 2), 3.32 (s, 3), and 3.08 (s, 3).

O-(*trans*-2-Butenyl) dimethylthiocarbamate* (**1d**) was obtained as a clear oil: nmr δ 5.71 (m, 2), 4.89 (broad d, J = 4 Hz, 1), 3.33 (s, 3), 3.10 (s, 3), and 1.72 (d, J = 5 Hz, 3).

O-Allyl dimethylthiocarbamate* (**1e**) was obtained as a clear oil: bp 42° (0.1 mm); nmr δ 6.1 (m, 1), 5.33 (broad d, J = 17 Hz, 1), 5.25 (broad d, J = 10 Hz, 1), 5.01 (broad d, J = 6 Hz), 3.37 (s, 3), and 3.17 (s, 3).

O-(1-Methylallyl) dimethylthiocarbamate* (**1f**) was obtained as a clear oil: nmr δ 5.97 (m, 2), 5.22 (m, 2), 3.33 (s, 3), 3.10 (s, 3), and 1.37 (d, J = 6 Hz, 3).

O-(1,2-Dimethylallyl) dimethylthiocarbamate* (**1g**) was isolated as a clear oil: nmr δ 5.98 (q, J = 7 Hz, 1), 5.01 (broad s, 1), 4.90 (broad s, 1), 3.35 (s, 3), 3.12 (s, 3), 1.78 (s, 3), and 1.38 (d, J = 7 Hz, 3).

O-(1-Hexen-3-yl) dimethylthiocarbamate* (**1h**) was eluted from the column as a clear oil: nmr δ 5.96 (m, 2), 5.27 (m, 2), 3.41 (s, 3), 3.20 (s, 3), and 2.0–0.7 (m, 7).

O-(2-Hexenyl) dimethylthiocarbamate* (**1i**) was obtained as a clear oil: nmr δ 5.72 (m, 2), 4.92 (d, J = 5 Hz, 2), 3.34 (s, 3), 3.10 (s, 3), 2.05 (m, 2), 1.4 (m, 2), and 0.9 (t, J = 6 Hz, 3).

O-(2-Ethyl-2-hexenyl) 1-piperidinecarbothioate* (**1j**) was obtained by the above procedure with the substitution of piperidine-*N*-thiocarbonyl chloride for dimethylthiocarbamoyl chloride. This carbamate was isolated as a clear oil: nmr δ 5.47 (broad t, J = 7 Hz, 1), 5.00 and 4.90 (singlets, cis and trans, 2), 3.87 (m, 4), 2.05 (m, 4), and 1.80–0.70 (m, 14).

O-(2-Cyclohexenyl) diethylthiocarbamate* (**1k**) was prepared by the above procedure using diethylthiocarbamoyl chloride, and characterized as a clear oil: nmr δ 5.90 (m, 3), 3.65 (septet, 4), 1.85 (m, 6), and 1.18 (m, 6).

Preparation of S-Allyl Dialkylthiocarbamates—Some S-allyl derivatives are obtained by rearrangement of O-allyl isomers *in situ*, while others are obtained from heating the purified O-allyl derivatives.

Sodium hydride (4.7 g, 57% in mineral oil) was washed with ether before 40 ml of DMF was added. Linalool (15.4 g) in DMF (40 ml) was added in portions, and the mixture was stirred under nitrogen for 1.5 hr. The mixture was cooled to 0°, and dimethylthiocarbamoyl chloride (12.4 g) in DMF (40 ml) was added. The ice bath was removed and the mixture was stirred at room temperature overnight. Work-up as above gave a mixture of 65% *trans*- and 35% *cis*-*S*-(3,7-dimethyl-2,6-octadienyl) dimethylthiocarbamate* (**2b**) (8 g) as a pale yellow oil: bp 110° (0.2 mm); nmr δ 5.2 (m, 2), 3.56 (d, J = 8 Hz, 2), 2.97 (s, 6), 2.07 (m, 4), and 1.66 (m, 9).

In the same manner, 2-methyl-3-buten-2-ol (15 g) yielded *S*-(3-methyl-2-butenyl) dimethylthiocarbamate* (**2l**) (10 g) as a clear oil: bp 74–76° (0.7 mm); nmr δ 5.28 (broad t, J = 8 Hz, 1), 3.55 (d, J = 8 Hz, 2), 2.97 (s, 6), and 1.70 (broad s, 6).

Diphenylethenylcarbinol was converted by the same procedure to *S*-(3,3-diphenyl-2-propenyl) dimethylthiocarbamate* (**2m**), isolated as a thick yellow oil: nmr δ 7.23 (m, 10), 6.23 (t, J = 8 Hz, 1), 3.62 (d, J = 8 Hz, 2), and 2.85 (s, 6).

4-Methyl-3-penten-2-ol was converted by the normal procedure to the *O*-carbamate **1n**, but, after standing at room temperature for several weeks, the product isolated was *S*-(2-methyl-3-penten-2-yl) dimethylthiocarbamate* (**2n**): bp 55–58° (0.2 mm); 90% trans; nmr δ 5.86 (d, J = 15.5 Hz, 1), 5.5 (m, 1), 2.92 (s, 6), 1.67 (d, J = 5 Hz, 3), and 1.56 (s, 6).

O-Geranyl dimethylthiocarbamate (**1a**) was heated without solvent at 140° for 2 hr to give in near-quantitative yield *S*-linalyl dimethylthiocarbamate* (**2a**). Final purification could be achieved by chromatography or distillation: bp 102–103° (0.3 mm); nmr δ ABC pattern 6.07 (A), 5.14 (B), 5.09 (C) (J_{AB} = 17.5, J_{AC} = 10, J_{BC} = 1 Hz), 5.1 (m, 1), 2.94 (s, 6), 1.97 (m, 4), 1.67 (s, 3), and 1.58 (s, 6).

O-Cinnamyl dimethylthiocarbamate (**1c**) heated at 130° for 2 hr gave *S*-(α-vinylbenzyl) dimethylthiocarbamate:* bp 113° (0.2 mm); nmr δ 7.31 (m, 5), 6.7 (m, 1), 5.2 (m, 3), and 2.88 (s, 6).

O-(*trans*-2-Butenyl) dimethylthiocarbamate (**1d**) was heated at 130° for 2 hr to give *S*-(1-buten-3-yl) dimethylthiocarbamate* (**2d**) as a clear oil: bp 55° (0.6 mm); nmr δ 5.98 (m, 1), 5.20 (split d, J = 17.5 Hz, 1), 5.07 (split d, J = 10 Hz, 1), 4.16 (m, 1), 2.98 (s, 6), and 1.54 (d, J = 7 Hz, 3).

O-Allyl dimethylthiocarbamate (**1e**) was heated at 140° for 2 hr to give *S*-allyl dimethylthiocarbamate[12] (**2e**): nmr δ 5.9 (m, 1), 5.2 (m, 2), 3.56 (d, J = 7 Hz, 2), and 2.98 (s, 6).

O-(1-Methylallyl) dimethylthiocarbamate (**1f**) was heated at 126° for 30 min to give *S*-(2-butenyl) dimethylthiocarbamate* (**2f**) (mixture of cis and trans) as a clear oil: nmr δ 5.60 (m, 1), 3.50 (broad d, J = 5 Hz, 2), 2.90 (s, 6), and 1.58 (broad d, J = 5 Hz, 3).

O-(1,2-Dimethylallyl) dimethylthiocarbamate (**1g**) was heated at 112° for 30 min to give *S*-(2-methyl-2-butenyl) dimethylthiocarbamate* (mixture of cis and trans) (**2g**) as a clear oil: nmr δ 5.53 (broad q, J = 6 Hz, 1), 3.57 (broad s, 2), 2.99 (s, 6), 1.66 (s, 3), and 1.57 (d, J = 6 Hz, 3).

O-(1-Hexen-3-yl) dimethylthiocarbamate (**1h**) was heated at 107° for 1.5 hr to give *S*-(2-hexenyl) dimethylthiocarbamate* (**2h**) (mixture of cis and trans) as a clear oil: nmr δ 5.57 (m, 2), 3.52 (broad d, J = 6 Hz, 2), 2.99 (s, 6), 1.98 (m, 2), 1.37 (m, 2), and 0.88 (m, 3).

O-(*trans*-2-Hexenyl) dimethylthiocarbamate (**1i**) was heated at 135° for 2 hr to give *S*-(1-hexen-3-yl) dimethylthiocarbamate (**2i**) as a clear oil: bp 67–68° (0.3 mm); nmr δ 5.9 (m, 1), 5.22 (two doublets, J_1 = 14, J_2 = 2 Hz, 1), 5.00 (two doublets, J_1 = 6, J_2 = 2 Hz, 1), 4.06 (q, J = 7 Hz, 1), 2.96 (s, 6), 1.6 (m, 4), and 0.9 (m, 3).

O-(2-Ethyl-2-hexenyl) 1-piperidinecarbothioate (**1j**) was heated at 130° for 2 hr to give *S*-[1-(1-methylenepropyl)butyl] 1-piperidinecarbothioate* (**2j**): bp 110–115° (0.2 mm); nmr δ 5.00 (broad s, 1), 4.88 (broad s, 1), 4.07 (t, J = 7 Hz, 1), 3.47 (m, 4), 2.16 (q, J = 7 Hz, 2), 1.6 (m, 10), and 1.03 (m, 6).

O-(2-Cyclohexenyl) diethylthiocarbamate (**1k**) was heated at 135° for 1 hr to yield *S*-(2-cyclohexenyl) diethylthiocarbamate* (**2k**) as a clear oil: bp 88–90° (0.2 mm); nmr δ 5.73 (m, 2), 4.17 (m, 1), 3.36 (q, J = 7 Hz, 4), 1.9 (m, 6), and 1.14 (t, J = 7 Hz, 6).

Preparation of Thiols.—The unsuccessful hydrolysis of **1b** with sodium hydroxide is described first, followed by a description of reduction with lithium aluminum hydride to give the desired thiol.

To *S*-linalyl dimethylthiocarbamate (1 g) was added methanol (15 ml), water (4 ml), and NaOH (0.3 g). The solution was stirred and heated under reflux under nitrogen overnight. The methanol was then removed under vacuum and water (15 ml) was added before extracting with ether (3 × 20 ml). The combined ether extracts were dried over $MgSO_4$ and the ether was removed under vacuum to leave a clear oil, which was shown by nmr to be about 60% starting material **1b** and 40% geranylthiol **4**.

To $LiAlH_4$ (3.8 g) in anhydrous ether (300 ml) was added dropwise *S*-linalyl dimethylthiocarbamate (21.1 g) in ether (150 ml) so as to maintain reflux. Stirring was continued while the mixture was heated under reflux for 2 hr. Water (4 ml) was then added, followed by 20% NaOH (3 ml), and water (14 ml). The solid was removed by filtration and washed with ether. The ether solution was dried over $MgSO_4$ and the ether was removed under vacuum to leave a clear oil (9.1 g), identified as linalylthiol **5**: bp 90° (15 mm); nmr δ ABC vinyl pattern 5.98 (A), 5.05 (B), 4.93 (C) (J_{AB} = 17, J_{AC} = 10, J_{BC} = 1 Hz), 2.3–1.5 (m, 4), 1.76 (s, 1), 1.67 (s, 3), 1.60 (s, 3), and 1.47 (s, 3).

S-(α-Vinylbenzyl) dimethylthiocarbamate was reduced in the same manner to give α-vinylbenzyl mercaptan as a clear oil: nmr δ 7.22 (m, 5), 6.11 (m, 1), 5.12 (two doublets, J_1 = 18, J_2 = 1 Hz, 1), 5.01 (two doublets, J_1 = 9, J_2 = 1 Hz, 1), 4.67 (overlapping doublets, $J_1 \cong J_2$ = 6 Hz, 1), and 1.97 (d, J = 6 Hz, 1).

Preparation of Nonadienes.—Given here is just one example of the sequence for synthesis of the nonadienes. Other compounds which have been employed include heterocyclic, cycloalkyl, and naphthyl groups in place of the methylenedioxyphenyl.

Linalyl mercaptan (9.6 g, 56 mmol) was added to a solution made by treating sodium (1.3 g, 56 mg-atoms) with methanol (100 ml). The solution was stirred under nitrogen and cooled to 0°, and piperonyl chloride (9.6 g, 56 mmol) was added in methanol (100 ml). Stirring was continued overnight at room temperature. The methanol was removed under vacuum, water (150 ml) was added, and the mixture was extracted with ether (2 × 100 ml). The ether extracts were combined and dried over $MgSO_4$ and the ether was removed under vacuum to leave a pale yellow oil. Chromatography over silica gel with hexane–benzene gave

(12) H. Tilles, *J. Amer. Chem. Soc.*, **81**, 714 (1959).

a clear oil (10.5 g), identified as linalyl piperonyl sulfide:* nmr δ 6.7 (m, 3), ABC pattern 5.86 (A), 5.08 (B), 4.95 (C) (J_{AB} = 11, J_{AC} = 17, J_{BC} = 1.5 Hz), 5.81 (s, 2), 5.1 (m, 1), 3.47 (s, 2), 2.0 (m, 2), 1.67 (s, 3), 1.59 (s, 3), 1.6 (m, 2), and 1.31 (s, 3).

The Grignard reagent for generating benzyne was made from magnesium (0.6 g, 25 mg-atoms) and 2-bromofluorobenzene (4.0 g, 23 mmol) in dry THF (50 ml). When the Grignard began forming, linalyl piperonyl sulfide was added (6.1 g, 20 mmol) in THF (25 ml). The solution was stirred under nitrogen and heated under reflux for 3 hr before cooling and adding saturated ammonium chloride (65 ml). The layers were separated and the aqueous layer was extracted with ether (75 ml). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under vacuum to leave a yellow oil. Chromatography over silica gel in hexane–benzene gave a clear oil (5.5 g), identified as 2,6-dimethyl-9-(3,4-methylenedioxyphenyl)-9-phenylthio-2,6-nonadiene: nmr δ 7.2 (m, 5), 6.7 (m, 3), 5.77 (s, 2), 5.1 (m, 2), 4.08 (t, J = 7 Hz, 1), 2.57 (t, J = 7 Hz, 2), 1.9 (m, 4), and 1.5 (m, 9).

2,6-Dimethyl-9-(3,4-methylenedioxyphenyl)-9-phenylthio-2,6-nonadiene (1 g) was stirred at room temperature for 30 min with W-2 Raney nickel[13] (5 ml settled) in ethanol (60 ml). The nickel was removed by filtration and the ethanol was removed under vacuum. The product was dissolved in ether (60 ml) and washed with water before drying over $MgSO_4$. Evaporation of ether and chromatography over silica gel in hexane–benzene gave a clear oil (0.7 g), identified as 2,6-dimethyl-9-(3,4-methylenedioxyphenyl)-2,6-nonadiene.* Glpc shows that the configuration at the central double bond is 70–75% trans and 25–30% cis. This sample is identical with that formed by another method[10] except for the cis:trans ratio: nmr δ 6.66 (s, 3), 5.86 (s, 2), 5.2 (m, 2), 2.4 (m, 4), 2.0 (m, 4), and 1.6 (d, 9).

Registry No.—**1a**, 39707-18-1; **1c**, 39707-19-2; **1d**, 39707-20-5; **1e**, 5513-30-4; **1f**, 39707-22-7; **1g**, 39707-23-8; **1h**, 39707-24-9; **1i**, 39707-25-0; *cis*-**1j**, 39707-26-1; *trans*-**1j**, 39707-27-2; **1k**, 39707-28-3; **2a**, 39707-29-4; *cis*-**2b**, 39707-30-7; *trans*-**2b**, 39707-31-8; **2c**, 39707-32-9; **2d**, 39707-33-0; **2e**, 18283-54-0; *cis*-**2f**, 39707-35-2; *trans*-**2f**, 39707-36-3; *cis*-**2g**, 39707-37-4; *trans*-**2g**, 39707-38-5; *cis*-**2h**, 39707-39-6; *trans*-**2h**, 39707-40-9; **2i**, 39707-41-0; **2j**, 39707-42-1; **2k**, 39707-43-2; **2l**, 39707-44-3; **2m**, 39707-45-4; **2n**, 39707-46-5; **5**, 39707-47-6; α-vinylbenzyl mercaptan, 39707-48-7; linalyl piperonyl sulfide, 39707-49-8; 2,6-dimethyl-9-(3,4-methylenedioxyphenyl)-9-phenylthio-2,6-nonadiene, 39707-50-1; *cis*-2, 6-dimethyl-9-(3,4-methylenedioxyphenyl)-2,6-nonadiene, 39707-51-2; *trans*-2,6-dimethyl-9-(3,4-methylenedioxyphenyl)-2,6-nonadiene, 39707-52-3; piperonyl chloride, 20850-43-5; 2-bromofluorobenzene, 1072-85-1.

Acknowledgment.—We wish to thank Mr. P. L. Unger and associates for spectral measurements and Mr. G. M. Maciak and associates for elemental analyses.

(13) R. Mozingo, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 181.

Studies on the Pinacol Rearrangement

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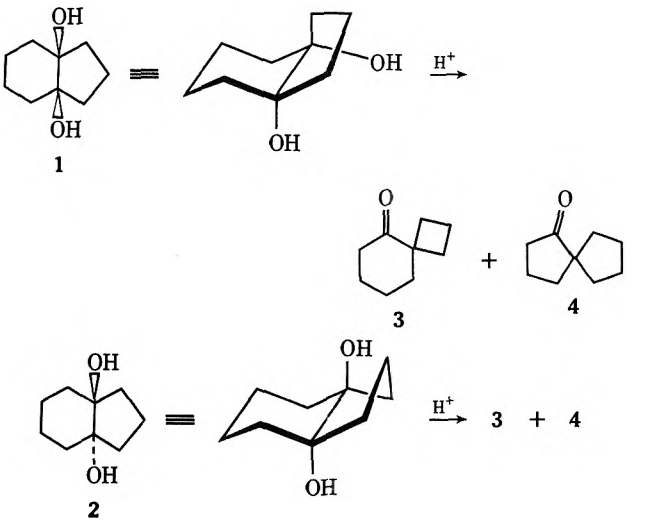
Received October 24, 1972

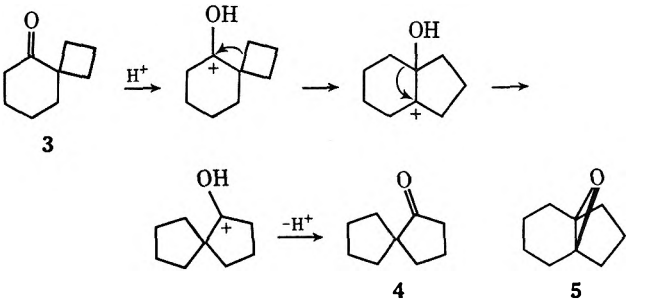
One of the interesting questions regarding the pinacol rearrangement is that concerned with stereochemical requirements. Curtin has demonstrated stereospecificity in semipinacolonic deaminations;[1] however, there exists a paucity of work regarding steric control for the pinacol rearrangement of glycols.[2]

The problem of stereochemistry can be best analyzed with conformationally homogeneous molecules. The *cis*- and *trans*-hydrindan system appeared suitable as a model system in view of the report by Fort that a carbonium ion generated at the ring fusion, under solvolytic conditions, maintained stereochemical integrity.[3]

We were prompted to examine the *cis*- and *trans*-8,9-dihydroxytetrahydroindan in the anticipation that a concerted pinacol rearrangement might be reflected in different product ratios for the two isomers. The glycols **1** and **2** have been previously prepared,[4] as have the spiranones **3**[5] and **4**.[6]



Treatment of either **1** or **2** with concentrated sulfuric acid at 0° for 10 min resulted in *complete* conversion to **4**. The epoxide **5**[3] could not be identified as a



reaction product; and a sample, when subjected to the reaction conditions, was shown to undergo rapid rearrangement to **4**. In testing whether **3** was stable to the reaction conditions, it was observed that **3** → **4**.

At this point the results can be rationalized by (a) glycol interconversion,[7] (b) unfavorable energetics for the formation of **3**, or (c) product instability.[8]

(1) D. Y. Curtin and M. C. Crew, *J. Amer. Chem. Soc.*, **77**, 354 (1955).
(2) B. P. Mundy and R. D. Otzenberger, *J. Chem. Educ.*, **48**, 431 (1971).
(3) R. C. Fort, Jr., R. E. Hornish, and G. A. Liang, *J. Amer. Chem. Soc.*, **92**, 7558 (1970).
(4) R. Criegee and H. Zogel, *Chem. Ber.*, **84**, 215 (1951).
(5) S. J. Etheredge, *J. Org. Chem.*, **31**, 1990 (1966).
(6) H. Christol, M. Mousseron, and M. F. Plenat, *Bull. Soc. Chim. Fr.*, **4**, 543 (1959).
(7) C. A. Bunton and M. D. Carr, *J. Chem. Soc.*, 5854 (1963).
(8) D. G. Botteron and G. Wood, *J. Org. Chem.*, **30**, 3871 (1965).

Unfortunately, these problems will always plague stereochemical studies of the pinacol rearrangement.

Experimental Section

The compounds discussed in this paper, **1–5**, have been reported elsewhere: **1** and **2**,[4] **3**,[5] **4**,[6] **5**.[3] Comparison of physical constants with those reported as well as the agreement of infrared and nmr spectra with the assigned structures confirmed the identity of the products.

General Procedure for Pinacol Rearrangement.—The glycol (0.1 g) was stirred with 5 ml of concentrated sulfuric acid. After 10 min the reaction mixture was poured into ice and water. The resulting aqueous solution was immediately extracted with methylene chloride, and the extracts were washed with 10% bicarbonate solution. The crude product was analyzed by analytical glc (6 ft × 6 mm glass column, packed with 16% hyprose SP 80 on 60–68 mesh Chromosorb W).

The spiranone **3** and the epoxide **5** were subjected to the same reaction conditions and work-up.

Registry No.—**1**, 39837-98-4; **2**, 39837-53-1; **4**, 14727-58-3.

Acknowledgments.—We are happy to acknowledge the financial support of the Endowment and Research Foundation of Montana State University, and the support of R. D. O. by a NDEA Predoctoral Fellowship, 1968–1971.

The Structures of Some of the Minor Alkaloids of *Cephalotaxus Fortunei*

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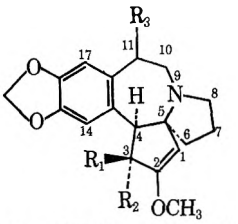
Received January 26, 1973

Some time ago[1] we reported on the isolation and partial structure elucidation of the major alkaloid of *Cephalotaxus fortunei* and *C. drupacea*, and named it cephalotaxine. Since this publication, the complete structure of cephalotaxine (**1**), as its methiodide, has been determined by X-ray crystallography,[2] and the alkaloid has been synthesized.[3,4]

Powell and coworkers[5] have also isolated, along with cephalotaxine, an ester of cephalotaxine, named harringtonine, which has shown significant inhibitory activity against experimental lymphoid leukemia systems L1210 and P388. Two minor alkaloids containing an oxygen function at R_3 in structure **1** have also been described.[5a]

We now wish to report on the isolation and structure

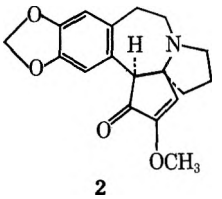


1, $R_1 = OH; R_2 = H; R_3 = H$
4, $R_1 = H; R_2 = OH; R_3 = H$

determination of some of the minor alkaloids of *Cephalotaxus fortunei*.

These minor alkaloids were obtained pure by careful column chromatography of the crude alkaloid mixture on neutral grade III alumina.

Alkaloid B.—This alkaloid was obtained in 1.08% yield of the crude alkaloid mixture. Its formula, as established by its mass spectrometric molecular weight and elemental analyses, is $C_{18}H_{19}NO_4$. Thus, it differs from cephalotaxine by having two fewer hydrogens. The infrared spectrum of this alkaloid, which is devoid of the hydroxyl absorption (3500 cm^{-1}) present in cephalotaxine, shows the presence of a carbonyl group (1720 cm^{-1}). Furthermore, the absorption due to the olefinic function in cephalotaxine (1665 cm^{-1}) is shifted to 1625 cm^{-1}. This bathochromic shift of the olefin absorption, in conjunction with the other observations (see Table I), suggests that alkaloid B is cephalotaxinone (**2**). It has now been shown that



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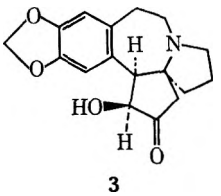
this alkaloid is also found in *C. harringtonia*.[5d] Furthermore, (±)-cephalotaxinone has recently been prepared as a key intermediate in the synthesis of racemic cephalotaxine,[3,4] and we have prepared it by Oppenauer oxidation of cephalotaxine (see Experimental Section).

Alkaloid C.—This minor alkaloid constitutes 5.4% of the crude alkaloidal mixture and is identical in every respect (infrared, ultraviolet, proton magnetic resonance spectrum, as well as by a mixture melting point determination) with an authentic sample of acetylcephalotaxine.[1] This alkaloid has also been isolated from *C. wilsoniana*.[1d]

Alkaloid D.—This compound is identical in every respect with demethylcephalotaxine (**3**), the product obtained by mild acid hydrolysis of cephalotaxine.[1]

Since cephalotaxine is stable to the conditions of isolation (as shown by subjecting it to the isolation procedure and recovering it without any loss), this alkaloid cannot be an artifact of isolation but is indeed present in the plant.



3

(1) (a) W. W. Paudler, G. I. Kerley, and J. McKay, *J. Org. Chem.*, **28**, 2194 (1963); (b) J. B. McKay, Ph.D. Thesis, Ohio University, Athens, Ohio, 1966; (c) J. Kerley, B.S. Honors Thesis, Ohio University, Athens, Ohio, 1964.

(2) D. J. Abraham, R. D. Rosenstein, and E. L. McGandy, *Tetrahedron Lett.*, 4085 (1969).

(3) J. Auerbach and S. M. Weinreb, *J. Amer. Chem. Soc.*, **94**, 7172 (1972).

(4) M. F. Semmelhack, B. P. Chong, and L. D. Jones, *J. Amer. Chem. Soc.*, **94**, 8629 (1972).

(5) (a) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and I. A. Wolff, *Tetrahedron Lett.*, 4081 (1969); (b) K. L. Mikolajczak, R. G. Powell, and C. R. Smith, Jr., *Tetrahedron*, **28**, 1995 (1972); (c) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and W. K. Rohweider, *Tetrahedron Lett.*, 815 (1970); (d) R. G. Powell, *Phytochemistry*, **11**, 1467 (1972); (e) R. G. Powell, *J. Pharm. Sci.*, **61**, 1227 (1972).

TABLE I

PMR DATA FOR SOME MINOR ALKALOIDS OF *Cephalotaxus drupacea*

Positions[a]	Alkaloid B (2) cephalotaxinone	Alkaloid C acetylcephalotaxine	Alkaloid D (3) demethylcephalotaxine	Alkaloid E (4) epicephalotaxine	Cephalotaxine[1] (1, R = H)
1	6.42	5.76	2.51 (2 H)	4.76 (s)	4.85
3		5.02 (d)	3.48	4.59 (d)	4.71 (d)
4	3.51	3.75 (d)	3.70	3.04 (d)	3.62 (d)
14	6.69	6.56	6.92	6.59	6.63
17	6.61	6.53	6.65	6.64	6.60
$-OCH_2O-$	5.88	5.82	5.92	5.79 (s)	5.83
$-OCH_3$	3.78	3.68		3.66 (s)	3.67
$-OCOCH_3$		2.20			
J_{34}		9.0	4.6	5.3	9.0

[a] The numbering of this ring system is delineated in structure 1. The pmr spectra were obtained as dilute solutions in $CDCl_3$ with a Varian HA-100 spectrometer. Chemical shifts are given in δ (parts per million).

Alkaloid E.—This minor alkaloid was obtained in 0.001% yield from the crude alkaloidal mixture. Its infrared spectrum is almost superimposable on that of cephalotaxine. It is, however, not cephalotaxine, since its melting point is depressed upon admixture with cephalotaxine. The physical properties of this alkaloid are identical with those of the minor product obtained from the lithium aluminum hydride reduction of cephalotaxinone.[6] Thus, it is reasonable to assign to this alkaloid the epicephalotaxine structure **4.**

Experimental Section

All infrared spectra were obtained on either a Perkin-Elmer Model 21 or Model 237 infrared spectrophotometer. The optical rotations were measured on a Rudolph polarimeter. Mass spectra on all of the compounds were obtained with a Hitachi Perkin-Elmer RMU-6D instrument and gave the correct molecular weights. Elemental analyses were done by Galbraith Laboratories, Inc., Knoxville, Tenn., and by the Analytical Services Laboratory of Ohio University. Chromatographic purity of all compounds was established by thin layer chromatography on silica gel G plates. The developing reagent was an aqueous potassium hexaiodoplatinate solution.

Isolation of Some of the Minor Alkaloids of *C. drupacea* (Table II).—A 31.1-g sample of the crude alkaloidal mixture of *Cephalotaxus drupacea* obtained as described in ref 1 was chromatographed on 1800 g of neutral grade III (Brockmann scale) alumina.

TABLE II

Fraction (12 ml/fraction)	Eluent	Weight, mg	Alkaloid
1–480	Benzene	0	
481–590	Benzene–ether (4:1)	0	
591–600	Benzene–ether	350	B
601–639	Benzene–ether	150	E + 3 compounds
640–1110	Benzene–ether	9910	cephalotaxine
1111–1120	Ether	400	F
1121–1169	Ether	0	
1170–1360	Ether–ethyl acetate (95:5)	841	G
1361–1612	Ethyl acetate	0	
1613–1622	Methyl alcohol	3730	C + other alkaloids
1623–1910	Methyl alcohol	9000	D + complex mixture

Alkaloid B.—The 350 mg (fractions 591–600) (1.08% of the crude alkaloidal mixture) of the crude alkaloid obtained from column chromatography was dissolved in ether and the hot suspension was filtered through 5.0 g of Brockmann grade V neutral alumina. The eluent was evaporated to a volume of 5 ml and allowed to stand at room temperature overnight. The white, crystalline solid which separated (75 mg) was recrystallized from ether (mp 198–200° dec, vacuum cap), $[\alpha]^{24}D$ −146° (*c* 0.63, $CHCl_3$). An additional 160 mg of this compound was obtained from further concentration of the ether solution. *Anal.* Calcd for $C_{18}H_{19}NO_4$: C, 68.97; H, 6.11; N, 4.5; O, 20.42. Found: C, 69.05; H, 6.37; N, 4.76. The infrared spectrum of this alkaloid as well as its pmr spectrum and chromatographic behavior are identical with those of cephalotaxinone.

Cephalotaxinone (2).—A solution of potassium *tert*-butoxide was prepared by dissolving 66 mg of potassium in 15 ml of *tert*-butyl alcohol. To this solution was then added 49 mg of cephalotaxine and 61 mg of benzophenone. The resulting solution was then refluxed for 10 hr and evaporated to near dryness under a stream of nitrogen. The residual material was partitioned between 20 ml of water and 20 ml of $CHCl_3$. The basic, aqueous layer was extracted with four 10-ml portions of 5% aqueous hydrochloric acid and the combined extracts were made basic with saturated aqueous Na_2CO_3. This solution was then extracted with two 20-ml portions of $CHCl_3$ and the combined extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness to yield 27 mg of a white solid which was recrystallized from ether to afford 18 mg of cephalotaxinone [mp 199.5–200.6° dec, vacuum cap; $[\alpha]^{24}D$ −155° (*c* 0.35, $CHCl_3$)]. This compound is identical in every respect with alkaloid B (infrared and pmr spectra, mixture melting point).

Alkaloid C.—The material obtained from the combined fractions 1613–1622 was dissolved in 50 ml of 5% aqueous HCl. The solution was filtered and the filtrate was made basic with solid Na_2CO_3. The precipitate which formed (678 mg) was filtered and dried (silica gel G). Tlc of this dark brown, amorphous material with 10:1 cyclohexane–diethylamine as solvent showed at least six components. The aqueous basic filtrate was extracted with four 50-ml portions of $CHCl_3$, the combined extracts were dried over anhydrous Na_2SO_4, and the filtrate was evaporated to dryness. The light yellow, amorphous solid (1.69 g) was found to be fairly basic ($pK_A' = 7.1$) and was obtained crystalline by recrystallization from ether. The resulting compound (mp 141–143°) is identical in every respect (infrared, pmr spectra, and mixture melting point) with acetylcephalotaxine as described in ref 1.

Alkaloid D.—The combined fractions 1623–1910 (9.00 g) were rechromatographed on neutral grade IV alumina. Elution with ether afforded 600 mg of a white, amorphous solid whose infrared spectrum shows absorption at 1705 cm^{-1}. The spectrum lacks the strong 1665-cm^{-1} absorption of the C=C function present in cephalotaxine. The compound gives a positive test with periodic acid.

The compound could, finally, be obtained crystalline by recrystallization from a small amount of ethanol to afford a solid, mp 109–111°, $[\alpha]^{25}D$ −110° (*c* 0.28, $CHCl_3$). This alkaloid is identical (nmr, infrared, tlc) in every respect with the acid hydrolysis product of cephalotaxine, identified as demethylcephalotaxine.

Demethylcephalotaxine.—This compound was described by us in an earlier paper, but had not been obtained in crystalline form at the time.[1] The amorphous material (100 mg) obtained by the procedure described in this paper was finally obtained crystalline by dissolving it in a minimum amount of absolute ethanol and allowing it to stand undisturbed in the refrigerator for 2 days.

The crystalline compound (70 mg) melted at 110–112.5°, $[\alpha]^{26}D$ −125° (*c* 0.60, $CHCl_3$). *Anal.* Calcd for $C_{17}H_{19}NO_4$: C, 59.45; H, 5.58; N, 16.32. Found: C, 59.20; H, 5.79; N, 16.58.

(6) It is of interest to note that reduction of cephalotaxinone with $NaBH_4$ or with diisobutylaluminum hydride has been reported to yield cephalotaxine exclusively.[4,5]

Alkaloid E.—The combined fractions 601–639 (150 mg) were rechromatographed on 500 g of neutral grade IV alumina; elution with benzene (200 ml) afforded 50 mg of a readily crystallizable alkaloid, mp 136–137°, $[\alpha]^{26}D$ −150° (*c* 0.8, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{21}NO_4$: C, 68.5; H, 6.72; N, 4.44. Found: C, 68.46; H, 6.49; N, 4.60. This alkaloid is identical in every respect (infrared, pmr, tlc) with the minor reduction product, epicephalotaxine, obtained from the reduction of cephalotaxinone.

Epicephalotaxine.—In a 50-ml flask of a micro Soxhlet extractor was placed 150 mg of cephalotaxinone and 40 ml of dry tetrahydrofuran. The solution was refluxed for 4 hr, and the condensing vapors were passed over 500 mg of lithium aluminum hydride contained in the extraction cup of the apparatus. The excess lithium aluminum hydride was then decomposed with saturated aqueous Na_2SO_4. The mixture was filtered and to the filtrate was added 200 ml of ether. The organic layer was then collected, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The remaining amorphous material (120 mg) was chromatographed on 200 g of neutral grade IV alumina. Slow chromatographic elution with benzene (75 ml) afforded 15 mg of epicephalotaxine, mp 135–137°. *Anal.* Calcd for $C_{18}H_{21}NO_4$: C, 68.5; H, 6.72; N, 4.44. Found: C, 68.38; H, 6.90; N, 4.60.

Further elution with benzene (300 ml) afforded a mixture (105 mg) of mainly cephalotaxine with only a trace of epicephalotaxine, as determined by tlc [R_f (epicephalotaxine)/R_f (cephalotaxine) 1.0–1.35, tlc silica gel plates, benzene].

Registry No.—**1**, 24316-19-6; **2**, 38750-57-1; **3**, 39707-71-6; **4**, 39707-72-7; acetylcephalotaxine, 24274-60-0; benzophenone, 119-61-9; tetrahydrofuran, 109-99-9.

Acknowledgment.—The partial financial support of this work by the National Science Foundation in the form of Grant G-25071 is gratefully acknowledged.

Thermal Decomposition of a Phenanthroxyl Quinol Ether. A Kinetic Study Using Laser Raman Spectroscopy

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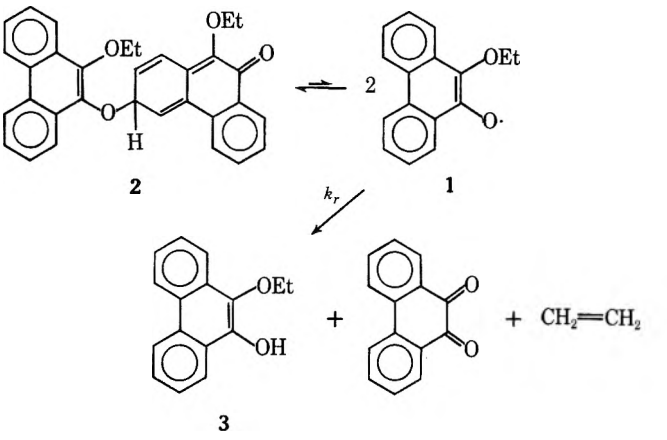
Received December 15, 1972

We have recently shown that the 10-ethoxy-9-phenanthroxyl radical **1** exists in equilibrium with its dimer **2** both in solution[2] and in the solid state,[3] and that the thermolysis of degassed samples of **2**, either in solution or as neat melts, leads to the slow formation of equimolar amounts of 10-ethoxy-9-phenanthrol (**3**), phenanthrenequinone, and ethylene.[2,3] This is thought to occur *via* disproportionation of **1**, as indicated in Scheme I, although unimolecular decomposition of **2** cannot be rigorously excluded. It is characteristic of this system and of other quinol ethers[4,5] that the ir, uv, and nmr spectra of the dimers and of the decomposition products are sufficiently complex and overlapped as to be useless for kinetic analysis of the decomposition; the usual recourse has been to monitor the concentration of radicals by esr.[2,5] We now wish to report that the thermolysis of **2** in degassed solution may be conveniently followed by laser Raman spectroscopy, which makes possible the direct monitoring of both **2** and **3**.

SCHEME I



In the course of routine laser Raman studies, it was noticed that spectra of *ca.* 0.1 *M* solutions of **2** in CCl_4 contained a peak at 1354 cm^{-1} attributable to **3** in addition to a peak at 1292 cm^{-1} characteristic of **2** (Figure 1). The frequency of the peak at 1292 cm^{-1} suggests that it is associated with the aryl ether C–O linkage in **2**; since the peak at 1354 cm^{-1} is also present in spectra of 10-chloro-9-phenanthrol, we infer that it is associated with the phenanthrol C–O bond. It should be noted that the positions of both peaks are insensitive to concentration and are, in fact, the same in solution as in the solid phase.

Since the amplitudes of the two peaks are proportional to the concentrations of **2** and **3**, it should in principle be possible to use the measured amplitudes directly for kinetic analysis. That turned out not to be true in this case; the high concentration of **2** required for the laser Raman spectra resulted in gradual precipitation of phenanthrenequinone as the decomposition progressed, causing excessive noise and base-line drift at reaction times longer than about 55 hr. As Table I shows, the observed amplitudes were unsuitable for direct analysis because of light scatter and base-line drift induced by the precipitate. However, since both peaks appear to arise from a vibrational mode of the aryl C–O group, it is not unreasonable to assume that the molar intensities of the two peaks are similar, if not equal. Given the known[2] 1:1 re-

TABLE I

NORMALIZATION OF LASER RAMAN KINETIC DATA[a]

	Observed amplitudes, mm				Normalized amplitudes, mm	
Time, hr	1292 cm^{-1}	1354 cm^{-1}	Sum	N^b	1292 cm^{-1}	1354 cm^{-1}
0.0	47	24	71	1.41	66	34
5.0	48	43	91	1.10	53	47
18.0	40	47	87	1.15	46	54
30.0	38	58	96	1.04	40	60
42.3	25	47	72	1.39	35	65
54.5	19	44	63	1.59	30	70

[a] Degassed 0.10 *M* solution in CCl_4 at 67°. [b] Normalization factor = 100/sum.

(1) Syva Research Institute, 3221 Porter Drive, Palo Alto, Calif. 94304.
(2) R. E. Schwerzel and J. E. Leffler, *J. Org. Chem.*, **37**, 3096 (1972).
(3) R. E. Schwerzel, Ph.D. Dissertation, Florida State University, 1970.
(4) D. J. Williams and R. Kreilick, *J. Amer. Chem. Soc.*, **90**, 2775 (1968).
(5) S. A. Weiner and L. R. Mahoney, *ibid.*, **94**, 5029 (1972).

lationship between the concentrations of 2 and 3, one may conclude that the *sum* of the observed amplitudes should ideally remain constant.[6] To correct the observed amplitudes, therefore, the sum at each time was normalized to a constant value (arbitrarily set at 100 mm); multiplying the observed amplitudes by the normalization factor $N = 100/\text{sum}$ at each time gave a set of normalized amplitudes which produced acceptable kinetic plots (Table I).[7,8]

As indicated in Table II, the values of the first-order rate constant k so obtained compare quite well with that previously obtained by esr measurements,[2,3,11]

TABLE II

SUMMARY OF THERMOLYSIS RATE DATA[a]

Analytical method	$[2]_0$,[b] M	10^6k,[c] sec^{-1}, ± 1.0
Laser Raman		
1292-cm^{-1} peak	0.10	3.2
1354-cm^{-1} peak	0.10	2.2
Esr[d]	0.02	1.3

[a] Degassed CCl_4 solutions at 67°. [b] Initial concentration of dimer. [c] First-order rate constant for the decomposition; see ref 11. [d] Reference 2.

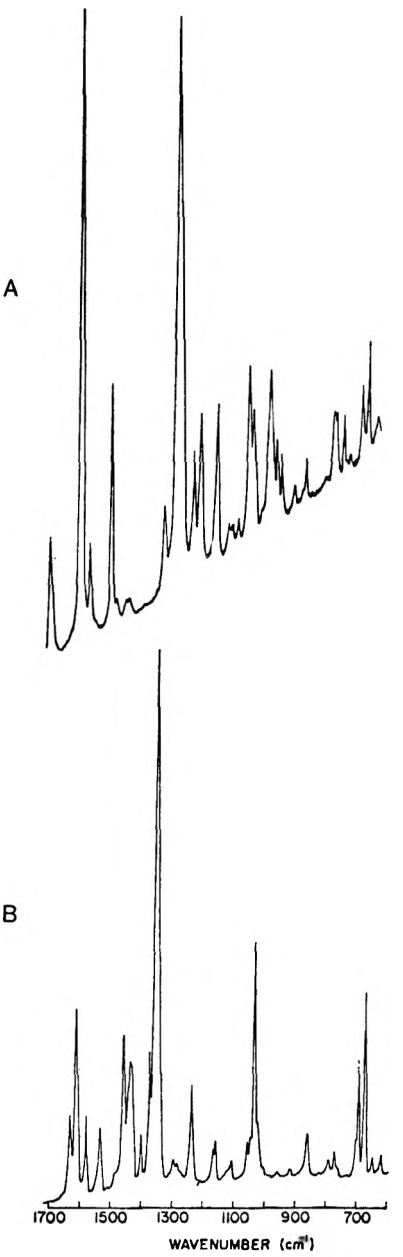


Figure 1.—Laser Raman spectra of (A) solid 2 and (B) solid 10-ethoxy-9-phenanthrol.

considering the differences in concentration and in method. We therefore feel that, in many cases, laser Raman spectroscopy will prove to be a useful adjunct to the more conventional techniques of kinetic analysis. This should apply particularly to those systems in which, as in the present case, the large number of ir-active vibrational modes renders the infrared spectrum useless as a kinetic tool.

Experimental Section[12]

Materials.—10-Chloro-9-phenanthrol, 10-ethoxy-9-phenanthrol, and the ethoxy dimer 2 were prepared as described previously.[2,3] Commercial spectroscopic grade CCl_4 was used as solvent for all runs.

(6) This is true even if the molar intensities of the two peaks are not precisely equal. The amplitude of the peak at 1292 cm^{-1} at any time t may be expressed as $A_2(t) = \alpha_2[\mathbf{2}]$, where α_2 is the molar intensity of the peak. Similarly, the amplitude of the peak at 1354 cm^{-1} is given by $A_3(t) = \alpha_3[\mathbf{3}]$. Since the stoichiometry of the reaction demands that $[\mathbf{2}] + [\mathbf{3}] = [\mathbf{2}]_0$, where $[\mathbf{2}]_0$ is the initial concentration of **2**, it is easily shown that

$$A_2(t) + A_3(t) = (\alpha_2 - \alpha_3)[\mathbf{2}] + \alpha_3[\mathbf{2}]_0$$

As long as α_2 and α_3 are of roughly the same magnitude it will be true that $(\alpha_2 - \alpha_3)[\mathbf{2}] \ll \alpha_3[\mathbf{2}]_0$, and to a good approximation the sum of the amplitudes will be constant: $A_2(t) + A_3(t) \cong \alpha_3[\mathbf{2}]_0$.

(7) It is important to recognize that this procedure in no way affects the value of the first-order rate constant, k, which is obtained from the plots. For instance, the normalized amplitude of the 1292-cm^{-1} peak at each time is given by

$$A_2' = NA_2 = A_2\left(\frac{100}{A_2 + A_3}\right) \cong [\mathbf{2}]\left(\frac{100\alpha_2}{\alpha_3[\mathbf{2}]_0}\right)$$

so that

$$\ln A_2' \cong \ln [\mathbf{2}] + \ln\left(\frac{100\alpha_2}{\alpha_3[\mathbf{2}]_0}\right)$$

Since the first-order decay of **2** is expressed by

$$\ln [\mathbf{2}] = \ln [\mathbf{2}]_0 - kt$$

it can be seen that a plot of $\ln A_2'$ *vs.* t is linear, with the same slope that would be obtained from a plot of $\ln [\mathbf{2}]$.

(8) A referee has objected to the fact that the points at $t = 0$ deviate considerably from the linear plot obtained for the remainder of the reaction. This troublesome behavior was also observed for esr kinetic runs carried out in commercial spectroscopic grade CCl_4, but *not* for esr runs carried out in benzene purified by the photochlorination technique of Saltiel.[9] The clear implication is that an impurity in the CCl_4 scavenges the radicals **1** during the early stages of the reaction. This is further supported by the observation that solutions of **2** in CCl_4, no matter how carefully prepared, always contained significant amounts of **3** as evidenced by the presence of a peak at 1354 cm^{-1}; this behavior made it impossible to accurately determine the molar intensity of the 1292-cm^{-1} peak. We consider that these observations are fully consistent with the recent report by Schuster and Weil[10] that commercial spectroscopic grade CCl_4, obtained from a variety of sources, contains varying amounts of 1,1-dichloropropene. This olefin should be an efficient scavenger for phenanthroxyl radicals such as **1**, with the decomposition proceeding normally once the supply of scavenger has been exhausted. Since the deviation of the point at $t = 0$ for a plot of the appearance of the peak at 1354 cm^{-1} (due to **3**) is roughly twice the deviation of the $t = 0$ point for a plot of the disappearance of the 1292-cm^{-1} peak, we infer that the scavenger serves as a hydrogen donor, giving two molecules of **3** per molecule of **2**.

(9) (a) J. Saltiel, H. C. Curtis, and B. Jones, *Mol. Photochem.*, **2**, 331 (1970); (b) J. Saltiel, private communication.

(10) D. I. Schuster and T. M. Weil, *Mol. Photochem.*, **4**, 447 (1972).

(11) The rate constant k for the disappearance of **2** (or the appearance of 10-ethoxy-9-phenanthrol) is related to k_r by $k = k_rK_{eq}$, where K_{eq} is the dissociation equilibrium constant. Assuming the process depicted in Scheme I, the rate law for disappearance of **1** is

$$\frac{-d[\mathbf{1}]}{dt} = \frac{k_rK_{eq}}{2}[\mathbf{1}]$$

so the value of k is easily extracted from esr data.[2,5]

(12) Laser Raman spectra were recorded on a Cary 81 Raman spectrophotometer, using a Spectra-Physics Model 125 He–Ne gas laser which produced an 80-mW beam at 632.8 nm. High-resolution mass spectra and mass measurements were obtained using an A. E. I. MS-902 double-focusing mass spectrometer equipped with a MSDS-II data reduction system.

Laser Raman Kinetics.—Routine laser Raman spectra of solutions were measured with the sample contained in a melting point capillary aligned coaxially with the laser beam. While 2 absorbed no light at the laser frequency, prolonged exposure to the beam (20–30 min) inevitably resulted in some deterioration of the sample. To minimize this problem in the kinetic study, the sample was contained in a 3-mm-o.d. Pyrex tube having one end flat; the other end was sealed after degassing the sample *in vacuo*. The larger diameter of this tube permitted thermal mixing of the solution in the vicinity of the laser beam, reducing the amount of laser-induced decomposition. The sample was kept in a thermostatted oil bath at 67.0 ± 0.1° and removed only long enough to record the two peaks for each point.

Registry No.—**1**, 38512-16-2; **2**, 35099-79-7; **3**, 35099-80-0.

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Communications

See Editorial, *J. Org. Chem.*, **37**, No. 19, 4A (1972).

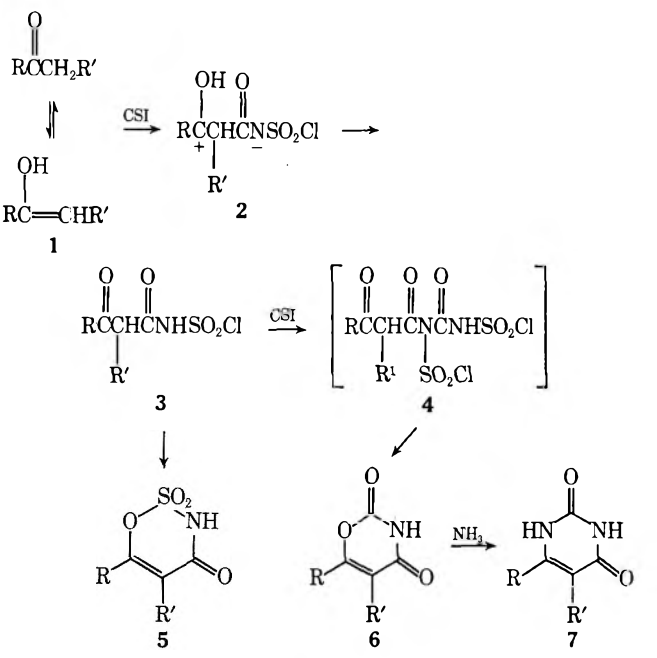
The Electrophilic Addition of Chlorosulfonyl Isocyanate to Ketones. A Convenient Synthesis of Oxazines, Oxathiazines, and Uracils[1]

Summary: CSI is found to react with ketones **1** in ether solution to produce 1,2,3-oxathiazines **5** and 1,3-oxazines **6** but, in CH_2Cl_2 solution, only **6** is formed; oxazines **6** are readily converted into uracils **7**.

Sir: Chlorosulfonyl isocyanate (CSI) has received considerable attention recently owing to its reactivity in various cycloadditions and its use in heterocyclic syntheses.[2] This remarkable electrophile reacts with a variety of compounds, including olefins,[2b] acetylenes,[2c] strained bicyclic hydrocarbons,[2d] and ketene thioacetals.[2e] Recent evidence[3a] has been interpreted mechanistically as involving $[{}_{\pi}2_s + {}_{\pi}2_a]$ cycloaddition of CSI to olefins; heterolytic ring opening of the initially formed β-lactam to a 1,4 dipole may then lead to rearranged products. However, 1,4 dipoles may still be the primary intermediates, giving 1,2 addition under kinetic control and rearranged products under thermodynamic control.[3b]

We wish to report the first examples of the electrophilic addition of CSI to simple ketones **1**,[4] a reaction which provides a facile entry into the 3,4-dihydro-4-oxo-1,2,3-oxathiazine 2,2-dioxide (**5**) and the 3,4-dihydro-2*H*-2,4-dioxo-1,3-oxazine (**6**) systems (Scheme I). The former represents a new heterocyclic system,[5] the novel reactions of which are currently under study.

SCHEME I



The latter are readily converted into uracil derivatives **7**.[6]

Treatment of **1**[7] with 2.3 equiv of CSI in ether or dichloromethane solution under nitrogen at room temperature for up to 7 days, followed by reductive hydrolysis with aqueous sodium sulfite solution,[8] provided **5** and **6** as the major isolated products (Table I).

As depicted in Scheme I, electrophilic addition of CSI to the enol form of **1** would produce the 1,4 dipole **2**,[9] which yields amide **3** by a proton shift. We have succeeded in trapping intermediate **3** by the isolation of various derivatives. These results will be described in our full paper. Reaction of **3** with a second equiva-

(1) Cycloadditions. XII. For paper XI, see A. Hassner and D. J. Anderson, *J. Amer. Chem. Soc.*, **94**, 8255 (1972).

(2) (a) For a recent review, see R. Graf, *Angew. Chem., Int. Ed. Engl.*, **7**, 172 (1968); (b) E. J. Moriconi and J. F. Kelly, *J. Org. Chem.*, **33**, 3036 (1968); E. J. Moriconi and W. C. Meyer, *ibid.*, **36**, 2841 (1971); L. A. Paquette, T. Kakihana, J. R. Hansen, and J. C. Phillips, *J. Amer. Chem. Soc.*, **93**, 152 (1971); L. A. Paquette, S. Kirschner, and J. R. Malpass, *ibid.*, **92**, 4330 (1970); (c) E. J. Moriconi and Y. Shimakawa, *J. Org. Chem.*, **37**, 196 (1972); (d) E. J. Moriconi and C. P. Dutta, *ibid.*, **35**, 2443 (1970); L. A. Paquette, G. R. Allen, Jr., and M. J. Broadhurst, *J. Amer. Chem. Soc.*, **93**, 4503 (1971); (e) F. A. Carey and J. R. Neergaard, *J. Org. Chem.*, **36**, 2731 (1971).

(3) (a) T. J. Barton and R. J. Rogido, *J. Chem. Soc., Chem. Commun.*, 878 (1972); T. J. Barton and R. J. Rogido, *Tetrahedron Lett.*, 3901 (1972); (b) J. R. Malpass and N. J. Tweddle, *J. Chem. Soc., Chem. Commun.*, 1244, 1247 (1972); J. R. Malpass, *ibid.*, 1246 (1972).

(4) CSI has been reported to react with a few β diketones such as dimedone and acetylacetone, leading to β-ketoamides. See ref 2a, p 180.

(5) The only previously reported examples appear to be the 5,6-dimethyl compound [K. Clauss and H. Jensen, *Tetrahedron Lett.*, 119 (1970)] and the 6-phenyl compound [K.-D. Kampe, *ibid.*, 123 (1970)].

(6) Satisfactory elemental analyses (+0.3%) were obtained for all new compounds, and the nmr, ir, and mass spectral data were in complete agreement with the structural assignments.

(7) Ketones in which neither R nor R′ is aryl appear to react in an entirely different manner. For example, 4-heptanone reacts with CSI in CH_2Cl_2 to yield butyric acid in 75% yield following work-up. Further investigation of this novel reaction is in progress.

(8) T. Durst and M. J. O'Sullivan, *J. Org. Chem.*, **35**, 2043 (1970).

(9) None of our experimental results, however, would preclude initial β-lactam formation followed by rapid ring opening to **2**.

TABLE I
REACTION OF KETONES 1 WITH CSI TO YIELD OXATHIAZINES 5 AND OXAZINES 6[a]

Compd	R	R'	Solvent	% 5	Mp, °C	% 6	Mp, °C
a	Ph	Me	Ether	41.5	122.5	28.4	184.5
			CH_2Cl_2			43.0	
b	Ph	Et	Ether	41.2	113–113.5	7.7	132.5–133
			CH_2Cl_2			14.8[b]	
c	Me	Ph	Ether			70.6	166.5
d	$PhCH_2$	Ph	Ether			61.0	137–137.5
e	Ph	Ph	Ether	28.4	233.5–234.5	13.6	220–222
f			Ether	30.3	258.5–260	19.8	210–211

[a] Yields are for pure isolated products. [b] After 11 days' reaction time; 2-benzoylbutyramide [J. Büchi, P. Schneeberger, and R. Lieberherr, *Helv. Chim. Acta*, **36**, 1402 (1953)] was also isolated from this reaction in 34.5% yield.

lent of CSI, cyclization, and hydrolysis on work-up leads to **6**. Alternatively, cyclization of **3** with loss of HCl would give oxathiazines **5**. Further mechanistic studies are in progress and will be detailed in our full paper.

Despite the biological importance of uracil derivatives, and the intense interest in their chemistry,[10] few examples are known containing alkyl or aryl substituents on both the 5 and 6 positions.[10,11] The ready availability of starting materials and the nearly quantitative conversion of oxazines **6** to uracils **7** by treatment with concentrated aqueous ammonia provide a new regiospecific two-step synthesis of 5,6-disubstituted uracils which is more advantageous than most conventional routes.[12]

Acknowledgment.—Support of this research by a grant from the National Science Foundation is gratefully acknowledged.

(10) D. J. Brown, "The Pyrimidines," Wiley-Interscience, New York' N. Y., 1962.

(11) (a) M. Draminski and B. Fiszer, *Rocz. Chem.*, **43**, 499 (1969); *Chem. Abstr.*, **70**, 115100v (1969). (b) M. Ohoka, S. Yanagida, and S. Komori, *J. Org. Chem.*, **37**, 3030 (1972).

(12) Reference 11, pp 31–115, 227–237.

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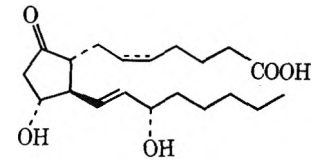
RECEIVED FEBRUARY 20, 1973

Syntheses of 11-Dehydro-13,14-dihydro-PGE$_1$ and PGD$_2$

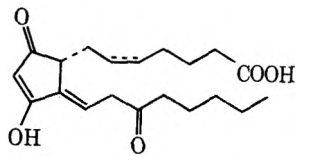
Summary: The syntheses of 11-dehydro-13,14-dihydro-PGE$_1$ (**9b**) and PGD$_2$ (**6b**) was achieved from diols **8** or **4**, respectively.

Sir: The formation of the triketo acid **2a** by oxidation of PGE$_1$ (**1a**) with Jones reagent has been reported by Pike, *et al.*[1] Similarly, we obtained the mixture of **2b** and **3**, at the ratio of 1:3 by oxidation of PGE$_2$ (**1b**) under the same condition (at 0°, for 20 min). **2b** had the following properties: uv $\lambda_{max}^{50\%\ EtOH}$ 282 nm; ir (liquid film) ν 3500–2500, 1707, 1560 cm^{-1}; nmr ($CDCl_3$) δ 6.50 (t, 1 H, C_{13} proton), 5.47 (s, 1 H, C_{10} proton), 5.35 (m, 2 H, C_5 and C_6 protons), 3.41 (d, 2 H, C_{14} protons). **3** had the following properties: uv $\lambda_{max}^{50\%\ EtOH}$ 231 nm; ir (liquid film) ν 3400, 3400–2500, 1740, 980 cm^{-1}; nmr ($CDCl_3$) δ 6.80 (dd, 1 H, C_{13} proton), 6.28 (d, 1 H, C_{14} proton), 5.38 (m, 2 H, C_5 and C_6 protons), 4.27 (q, 1 H, C_{11} proton).

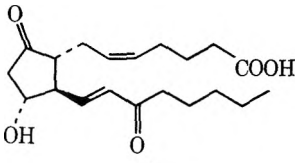
5 was formed, together with **6a** and **7a**, by oxidation of **4** under the same condition. There is a presumption that migration of the trans double bond to C_{12} will lower PG-like biological activity, and it is known that the saturation of the trans double bond to single bond retains its activity.[2] For these reasons we have synthe-



1a, no 5,6 double bond
b, 5,6 double bond



2a, no 5,6 double bond
b, 5,6 double bond



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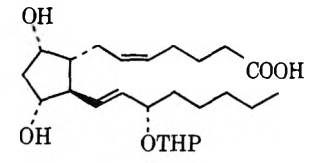

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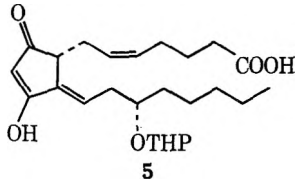
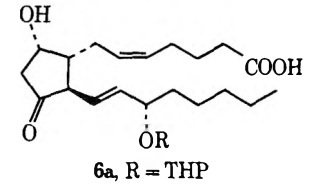
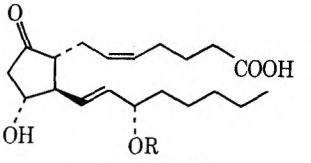


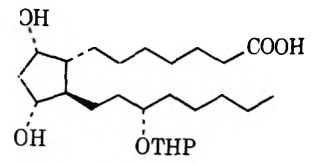
5



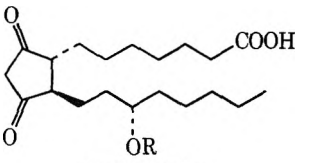
6a, R = THP
b, R = H



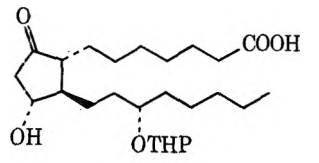
7a, R = THP
b, R = H



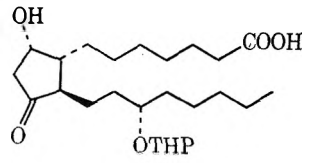
8



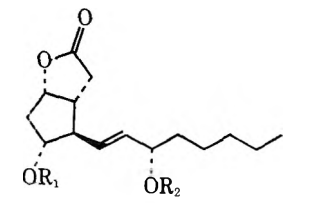
9a, R = THP
b, R = H



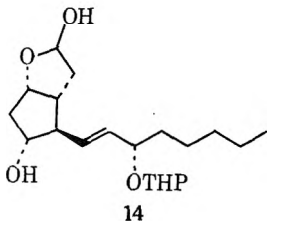
10



11



12, $R_1 = COCH_3$; $R_2 = H$
13, $R_1 = COCH_3$; $R_2 = THP$



14

(1) J. E. Pike, F. H. Lincoln, and W. P. Schneider, *J. Org. Chem.*, **34**, 3552 (1969).

(2) E. Ånggard, *Acta Physicol. Scand.*, **66**, 509 (1966).

sized **9b**. **9a** was obtained by oxidation of **8** with Jones reagent in 42% yield after purification. **10** and **11** were also obtained by oxidation of **8** by the same procedure.

Hydrolysis of **9a** in AcOH–H_2O (2:1) at 40° for 2 hr afforded 11-dehydro-13,14-dihydro-PGE_1 (**9b**): uv $\lambda_{max}^{50\%\ EtOH}$ 245 nm; ir (*liquid film*) ν 3600–2200, 1705, 1660, 1580 cm^{-1}; nmr ($CDCl_3$) δ 5.13 (s, 1 H, C_{10} proton); 48% yield. **9b** exists in the enolic form on the basis of ir and nmr data and does not show the PG-like biological activity.

Oxidation of **4** with Jones reagent under a mild condition (*at −30° for 15 min*) gave a mixture of **6a** and **7a** along with a trace of **5** in 75% total yield. It is very interesting that **6a** and **7a** are formed in a ratio of 2–3:1. **6a** was isolated from the mixture of **6a** and **7a** by column chromatography on silica gel (**6a** is less polar than **7a**) and hydrolyzed into PGD_2 (**6b**) in AcOH–H_2O (2:1) at 40° for 2 hr in 45% yield. **6b** was obtained as white crystals: mp 68° (recrystallized from EtOAc–*n*-hexane); ir (KBr) ν 3400–2500, 1740, 1700, 975 cm^{-1}; nmr ($CDCl_3$) δ 5.32 (m, 4 H, olefinic protons), 4.48 (m, 1 H, C_9 proton), 4.12 (m, 1 H, C_{15} proton), 2.83 (dd, 1 H, $C_{10\beta}$ proton), 2.42 (m, 1 H, $C_{10\alpha}$ proton), 2.43 (m, 1 H, C_8 proton). Similarly, PGE_2 (**7b**) was formed by hydrolysis of **7a**.[3]

(3) Ir, nmr, and R_f value on tlc were completely the same as those of authentic PGE_2.

PGD is one of the by-products in the biosynthesis of PGE.[4] The isolation and determination of the structure of PGD[4] have been already reported, but the chemical synthesis of PGD has not yet been reported.

The starting material **4** was obtained as follows. **12**[5] was converted into **13** quantitatively using 1.5 equiv of 2,3-dihydropyran and a catalytic amount of *p*-toluenesulfonic acid in methylene chloride at 25° for 15 min. Reduction of **13** by means of 5 equiv of diisobutylaluminum hydride in toluene at −60° for 15 min afforded **14** in 95% yield. **4** was formed by Wittig reaction of **14** with 4-carboxy-*n*-butylidenetriphenylphosphorane[6] in dimethyl sulfoxide in 68% yield.

8 was obtained by catalytic reduction of **4** with PtO_2 in ethanol at room temperature in 92% yield.

(4) E. Granström, W. E. Lands, and B. Samuelsson, *J. Biol. Chem.*, **243**, 4104 (1968); P. S. Foss, C. J. Sih, C. Takeguchi, and H. Schnoes, *Biochemistry*, **11**, 2271 (1972).

(5) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Amer. Chem. Soc.*, **92**, 397 (1970).

(6) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

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GAS CHROMATOGRAPHIC TOOLS

While gas chromatography (GC) has become a highly useful analytical tool, many compounds, such as amino acids, carbohydrates and steroids, cannot be analyzed by GC because they either decompose at the high column temperatures necessary for volatilization or require excessively long elution times. This difficulty can be overcome by the preparation of trimethylsilyl derivatives[1] since their greater volatility facilitates GC analysis.

We offer two excellent reagents: *bis(trimethylsilyl)acetamide*[2] and *bis(trimethylsilyl)trifluoroacetamide*[3], for simple preparations of trimethylsilyl derivatives often in virtually quantitative yield. BSA and BSTFA readily silylate such slightly volatile compounds[4] as amides, ureas, amino acids, phenols, carboxylic acids and enols. In addition, BSA and BSTFA can be used in the GC analysis of many water-soluble substances of biological interest, such as sugar phosphates,[5] hexosamines,[6] hexosaminitols,[7] nucleic acid bases and nucleosides.[8] Since these reagents are generally used in excess, BSTFA is more useful than BSA in some instances. BSTFA has greater volatility, higher solubility in many solvents and gives lower detector response and less detector contamination. In the case of some amino acids, such as glycine and alanine, GC analysis is possible only with BSTFA.

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12,891-0	**Bis(trimethylsilyl)acetamide (BSA)**	**10g**	**3.75**
		25g	**8.00**
		100g	**28.00**
15,519-5	**Bis(trimethylsilyl)trifluoroacetamide (BSTFA)**	**5g**	**7.60**
		25g	**25.20**
		100g	**67.10**

ORGANOSILICON REAGENTS

One of the best known organosilicon compounds is tetramethylsilane (TMS), a widely used nmr standard. We offer TMS of the highest quality, carefully purified to remove any ether impurities which are detrimental to lanthanide chemical shift reagent studies.

In addition, we now offer a variety of silanes which allows the synthetic chemist to explore the new and exciting possibilities ot organosilicon chemistry.[1]

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C7285-4	Chlorotrimethylsilane	100g	4.75	500g	10.00
D6082-6	Dichlorodimethylsilane	100g	4.50	129.1gt	6.00	500g	6.85
H1000-2	1,1,1,3,3,3-Hexamethyldisilazane	25g	3.00	100g	10.00
T2400-7	Tetramethylsilane, 99.9%	25g	11.70	100g	31.20
11,339-5	3-Aminopropyltriethoxysilane			100g	8.40
17,556-0	Triethoxyvinylsilane	100g	4.25	500g	13.00
17,558-7	Tris(2-methoxyethoxy)vinylsilane	250g	7.00	1Kg	20.00
17,561-7	Mercaptopropyltrimethoxysilane	50g	4.80	250g	16.00

† Designates Molar Units

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