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THE JOURNAL OF Organic Chemistry®

VOLUME 37, NUMBER 9 MAY 5, 1972

ERLING GROVENSTEIN, JR.,* JAMES A. BERES, YAO-MING CHENG, AND JAMES A. PEGOLOTTI 1281 Carbanions. XI. Reactions of 4-Chloro-1,1,1-triphenylbutane, 5-Chloro-1,1,1-triphenylpentane, and 1,1,1-Triphenylethane with Alkali Metals. 1,4 and 1,5 Migration of Phenyl

E. GHERA* AND S. SHOUA 1292 The Influence of Chelation on the Grignard Reactions of Some β-Hydroxy Ketones

CLAYTON H. HEATHCOCK* AND BRUCE E. RATCLIFFE 1298 Acid-Catalyzed Rearrangement of 6-Methyltricyclo[4.4.0.0^{2,7}]decan-3-one

RICHARD N. MCDONALD,* D. G. FRICKEY, AND GARY M. MUSCHIK 1304 Strained Ring Systems. XI. The Synthesis of Benzobicyclo[2.2.0]hexa-2,5-diene, Benzobicyclo[2.2.0]hex-2-ene, and Benzobicyclo[2.2.0]hex-5-en-*exo*-2-ol

HUGH W. THOMPSON* AND RICHARD E. NAIPAWER 1307 Synthesis of Angularly Substituted Tetrahydro- and Hexahydrofluorenes

MELVIN S. NEWMAN* AND CHIN H. CHEN 1312 The Resolution and Absolute Configuration of 7-Methylhexahelicene

F. J. WEIGERT 1314 The Conformations of Electronegatively Substituted Imines

BETTY R. LOWRY AND ALAIN C. HUITRIC* 1316 7,8,9-Trimethoxy-4a,10b-*trans*- and -4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridines. Configurational and Conformational Changes in Epimerization of N-Substituted Derivatives

FRANK W. FOWLER 1321 Synthesis of 1,2- and 1,4-Dihydropyridines

SISIR K. SENGUPTA,* SUPRABHAT CHATTERJEE, H. KANGUR PROTOPAPA, AND EDWARD J. MODEST 1323 2,4-Diaminopyrimidines from Dicyandiamide. IV. Condensation with Bicyclic Aromatic Ketones

GEORGE R. NEWKOME* AND D. L. FISHEL 1329 Pyrolysis of Ketone *N,N,N*-Trimethylhydrazonium Fluoborates. Evidence for the Genesis of Pyridines

JOHN H. SELLSTEDT 1337 2-Pyrones from Condensation of β-Keto Esters with 1,3 Diketones in Trifluoroacetic Acid. A Correction of the Literature

J. F. HARRIS, JR. 1340 α- and β-(Trifluoromethylthio)acrylic Acid Derivatives

MAYNARD S. RAASCH 1347 Bis(trifluoromethyl)thioketene. II. Acyclic Derivatives

O. FRANCIS BENNETT,* M. J. BOUCHARD, RICHARD MALLOY, PETER DERVIN, AND GERALD SALUTI 1356 Hydroxide Displacement of the Sulfone Linkage in Thioxanthen-9-one 10,10-Dioxides to Benzophenone-2′-hydroxy-2-sulfinic Acids. Intramolecular Cyclization to Xanthones

J. H. BOYER* AND V. T. RAMAKRISHNAN 1360 Sulfurization of Isocyanides

Z. YOSHIDA,* S. YONEDA, AND M. HAZAMA 1364 Reactions of Dimethylsulfonium Cyclopentadienylide with Electrophiles and Dienophiles

DAVID N. HARPP* AND P. MATHIAPARANAM 1367 The 1,3,2-Dioxaphospholene–Sulfenyl Chloride Condensation. Scope and Mechanism

S. N. SINGH AND M. V. GEORGE* 1375 Photochemical and Thermal Transformations of *O*-Alkyl *S*-Phthalyl Xanthates and Dithiocarbamyl Phthalides

S. L. JOHNSON* AND H. M. GIRON 1383 Nucleophilic Reactivity to Diphenylcarbamoyl Derivatives. The Unimolecular Nature of Diphenylcarbamoyl Chloride Hydrolysis

C. A. BUNTON,* A. KAMEGO, AND M. J. MINCH 1388 Micellar Effects upon the Decarboxylation of 3-Bromo and 2-Cyano Carboxylate Ions

DALE E. VAN SICKLE 1392 Autoxidation of Esters. I. Isobutyl Acetate

DALE E. VAN SICKLE 1398 Autoxidation of Esters. II. Cyclohexylenedimethylene Diacetate

WERNER HERZ* AND R. C. LIGON 1400 Resin Acids. XXIII. Oxidation of Levopimaric Acid with Potassium Permanganate and Osmium Tetroxide

SHUKICHI YAMANA 1405 Molecular Rotations of Steroids in Relation to Their Structures. The *S* Value of a Hydrogen Atom and That of a Hydroxyl Radical

Anatoli Onopchenko, Johan G. D. Schulz,* and Richard Seekircher	1414	Nonclassical Oxidation of Aromatics. I. Cobaltic Ion Catalyzed Oxidations of *p*-Cymene, *p*-Ethyltoluene, and *sec*-Butyltoluenes
Carmen V. Smith, Roland K. Robins, and Richard L. Tolman*	1418	Synthesis of 1-β-D-Arabinofuranosylorotate and an Investigation of the Rearrangement of 2,2′-Anhydroorotidine Derivatives
K. T. Potts* and M. Sorm	1422	Mesoionic Compounds. XVI. 1,4-Dipolar Type Cycloaddition Reactions Utilizing Pyrimidinium Betaines
Stephen A. Haut, Dorothy C. Schroeder, and J. P. Schroeder*	1425	Liquid Crystals. II. Unsymmetrical *p*-Phenylene Di-*p*-*n*-alkoxybenzoates
Giulio Cauzzo* and Giulio Jori	1429	Methylene Blue Photosensitized Conversion of 3-Substituted Indoles to β-Carboline Derivatives
Luciano do Amaral	1433	Mechanism and Catalysis for Furfural Phenylhydrazone Formation
Peggy J. Duke and David W. Boykin, Jr.*	1436	The Influence of Configuration on Transmission of Electronic Effects in α,β-Unsaturated Ketones

NOTES

David B. Ledlie	1439	The Rearrangement of 11,11-Dibromotricyclo[4.4.0.$0^{1,6}$]undecane
John A. Katzenellenbogen and E. J. Corey*	1441	A Novel Cyclization Mediated by Organocopper Reagents
F. D. Saeva	1442	Mechanism of the Base-Catalyzed Condensation of Naphthols with 2,3-Dichloro-1,4-naphthoquinone
Herbert M. Rosenberg* and M. Paul Servé	1443	Reaction between Arylnitrones and Arylnitroso Compounds
Luisito Tolentino and Jacques Kagan*	1444	On the Friedel–Crafts Benzoylation and Acylation of Kojic Acid
David A. Nelson	1447	Synthesis of *cis*- and *trans*-3-Chloroazetidinones. II. Direct Acylation of Imines
C. Hackett Bushweller,* George E. Yesowitch, and Frank H. Bissett	1449	The *A* Value of the Deuterioamino Group Determined by the Nuclear Magnetic Resonance Peak Area Method at −93°
T. Kametani,* K. Kigasawa, M. Hiiragi, and T. Aoyama	1450	Studies on the Syntheses of Heterocyclic Compounds. CDLX. Benzyne Reaction. XIII. Benzyne Reaction of Halogenobenzenes with *N*-Alkylmorpholines
Leonard F. Bjeldanes and Henry Rapoport*	1453	A Bisulfite Mediated Oxidation of Thebaine. Formation of 6-*O*-Demethylsalutaridine
Kenneth B. Wagener, S. Richard Turner, and George B. Butler*	1454	A Novel Intramolecular Rearrangement of a 1,4 Dipole
George J. Kasperek and Thomas C. Bruice*	1456	Intramolecular Catalysis in the Aminolysis of Thiol Esters
D. R. Maulding* and B. G. Roberts	1458	The Chemiluminescence of Tetrachloroethylene Carbonate and Related Compounds
G. E. Voecks, P. W. Jennings,* G. D. Smith, and C. N. Caughlan	1460	Thermal and Photochemical Dimerization of Norbornadiene Using Tetracarbonylnickel as a Catalyst
Richard J. Spangler* and J. C. Sutton	1462	The Photochemistry of 1-Keto-2-carbomethoxymethylenebenzocyclobutene
Howard Alper* and Edmund C. H. Keung	1464	A New Synthesis of the 1,3-Thiazine Ring System
Eugene I. Snyder	1466	Conversion of Allylic Alcohols to Chlorides without Rearrangement

AUTHOR INDEX

Alper, H., 1464
Aoyama, T., 1450

Bennett, O. F., 1356
Beres, J. A., 1281
Bissett, F. H., 1449
Bjeldanes, L. F., 1453
Bouchard, M. J., 1356
Boyer, J. H., 1360
Boykin, D. W., Jr., 1436
Bruice, T. C., 1456
Bunton, C. A., 1388
Bushweller, C. H., 1449
Butler, G. B., 1454

Caughlan, C. N., 1460
Cauzzo, G., 1429
Chatterjee, S., 1323
Chen, C. H., 1312
Cheng, Y.-M., 1281
Corey, E. J., 1441

Dervin, P., 1356
do Amaral, L., 1433
Duke, P. J., 1436

Fishel, D. L., 1329
Fowler, F. W., 1321
Frickey, D. G., 1304

George, M. V., 1375
Ghera, E., 1292
Giron, H. M., 1383
Grovenstein, E., Jr., 1281

Harpp, D. N., 1367
Harris, J. F., Jr., 1340
Haut, S. A., 1425
Hazama, M., 1364
Heathcock, C. H., 1298
Herz, W., 1400
Hiiragi, M., 1450
Huitric, A. C., 1316

Jennings, P. W., 1460
Johnson, S. L., 1383
Jori, G., 1429

Kagan, J., 1444
Kamego, A., 1388
Kametani, T., 1450
Kasperek, G. J., 1456
Katzenellenbogen, J. A., 1441
Keung, E. C. H., 1464
Kigasawa, K., 1450

Ledlie, D. B., 1439
Ligon, R. C., 1400
Lowry, B. R., 1316

Malloy, R., 1356
Mathiaparanam, P., 1367
Maulding, D. R., 1458
McDonald, R. N., 1304
Minch, M. J., 1388
Modest, E. J., 1323
Muschik, G. M., 1304

Naipawer, R. E., 1307
Nelson, D. A., 1447
Newkome, G. R., 1329
Newman, M. S., 1312

Onopchenko, A., 1414

Pegolotti, J. A., 1281
Potts, K. T., 1422
Protopapa, H. K., 1323

Raasch, M. S., 1347
Ramakrishnan, V. T., 1360
Rapoport, H., 1453
Ratcliffe, B. E., 1298
Roberts, B. G., 1458
Robins, R. K., 1418
Rosenberg, H. M., 1443

Saeva, F. D., 1442
Saluti, G., 1356
Schroeder, D. C., 1425
Schroeder, J. P., 1425
Schulz, J. G. D., 1414
Seekircher, R., 1414
Sellstedt, J. H., 1337
Sengupta, S. K., 1323
Servé, M. P., 1443
Shoua, S., 1292
Singh, S. N., 1375
Smith, C. V., 1418
Smith, G. D., 1460
Snyder E. I., 1466
Sorm, M., 1422
Spangler, R. J., 1462
Sutton, J. C., 1462

Thompson, H. W., 1307
Tolentino, L., 1444
Tolman, R. L., 1418
Turner, S. R., 1454

Van Sickle, D. E., 1392, 1398
Voecks, G. E., 1460

Wagener, K. B., 1454
Weigert, F. J., 1314

Yamana, S., 1405
Yesowitch, G. E., 1449
Yoneda, S., 1364
Yoshida, Z., 1364

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VOLUME 37, NUMBER 9

MAY 5, 1972

Carbanions. XI. Reactions of 4-Chloro-1,1,1-triphenylbutane, 5-Chloro-1,1,1-triphenylpentane, and 1,1,1-Triphenylethane with Alkali Metals. 1,4 and 1,5 Migration of Phenyl[1,2]

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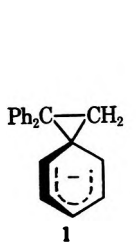
Received August 31, 1971

Whereas 1,2 migrations of phenyl are known in carbanions, corresponding 1,4 and 1,5 migrations have not been reported. In the present work such rearrangements were looked for in the reactions of 4-chloro- and 5-chloro-1,1,1-triphenylalkanes with alkali metals. Reaction of 4-chloro-1,1,1-triphenylbutane with lithium in tetrahydrofuran (THF) at −50 to −60° gives 4,4,4-triphenylbutyllithium; when the latter is warmed to 25° 1,1,1-triphenylbutane, but no detectable products of rearrangement, is obtained. With potassium metal in THF at reflux temperature, this chloride gives chiefly 1,1-diphenyl-1,2,3,4-tetrahydronaphthalene; with Cs-K alloy at −49°, the initial product is 1,1,1-triphenylbutane along with some 9% of 1,1,4-triphenylbutyl anion (product of 1,4-phenyl migration). Reaction of 5-chloro-1,1,1-triphenylpentane with potassium or with Cs-K and Cs-K-Na alloys in THF gives primarily 1,1,1-triphenylpentane as initial product along with (for cesium alloys) some 6% of a product of 1,5 migration of phenyl. 2-Chloro-1,1,1-triphenylethane with Cs-K-Na alloy in THF at −65° gives chiefly 1,1,2-triphenylethyl anion (product of 1,2-phenyl migration). Reaction of 1,1,1-triphenylethane with Cs-K-Na alloy in THF at −70° gives a novel red dianion which upon protonation gives 9-methyl-9-phenyl-2,4a,4b,7-tetrahydrofluorene in high yield as a single stereoisomer. Similar reactions occur with 1,1,1-triphenylbutane and 1,1,1-triphenylpentane. These reactions and some of the interesting variations with choice of alkali metal are discussed in terms of likely mechanisms. The synthetic utility of cesium alloys is emphasized.

Previous work has shown that 2,2,2-triphenylethyllithium[4] in tetrahydrofuran solution undergoes rearrangement to 1,1,2-triphenylethyllithium by an intramolecular process,[5a] apparently *via* a cyclic transition state or reaction intermediate[5b] such as **1**. In view of



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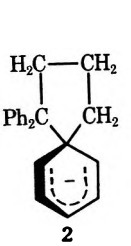

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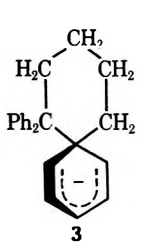


3

the observed ready 1,2 migration of phenyl in this and other carbanions,[6] it would be expected that corresponding 1,4 and 1,5 migrations of phenyl might also occur, thus *via* **2** and **3**, respectively. The present work was undertaken to test these possibilities.

(1) Abstracted in part from the M.S. Thesis of Y.-M. Cheng, Georgia Institute of Technology, 1967.

(2) Presented in part at Metrochem 69, Regional Meeting of the American Chemical Society, New York, N. Y., May 2, 1969.

(3) National Science Foundation Summer Faculty Research Participant.

(4) E. Grovenstein, Jr., and L. P. Williams, Jr., *J. Amer. Chem. Soc.*, **83**, 412 (1961).

(5) (a) E. Grovenstein, Jr., and G. Wentworth, *ibid.*, **89**, 1852 (1967); (b) *ibid.*, **89**, 2348 (1967).

(6) See also H. E. Zimmerman and A. Zweig, *ibid.*, **83**, 1196 (1961).

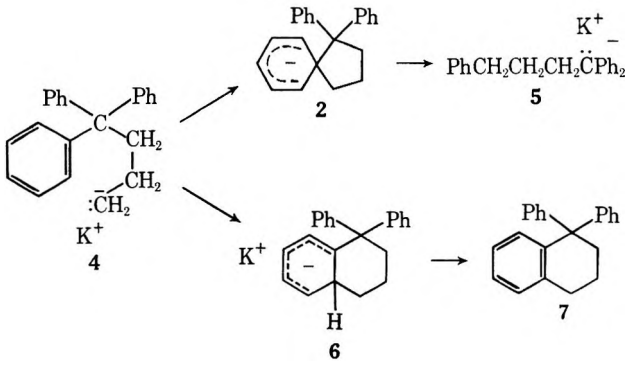
Results and Discussion

Reactions of 4-Chloro-1,1,1-triphenylbutane with Alkali Metals.—Lithium metal reacts with 4-chloro-1,1,1-triphenylbutane in tetrahydrofuran at −50 to −60° to give 4,4,4-triphenylbutyllithium, as deduced from carbonation which gave 5,5,5-triphenylpentanoic acid. Attempts to effect thermal rearrangement of this organolithium compound to 1,1,4-triphenylbutyllithium in tetrahydrofuran solution at 0° or at 25° were unsuccessful, although a temperature of 0° had proven adequate for rearrangement of 2,2,2-triphenylethyllithium.[4] The reaction at 25° gave upon carbonation a product which contained predominantly neutral products and only 4% by weight of acidic material in which 46% of 5,5,5-triphenylpentanoic acid, but no 2,2,5-triphenylpentanoic acid, was found. The volatile neutral material contained predominantly 1,1,1-triphenylbutane and a little starting chloride. Thus, 4,4,4-triphenylbutyllithium in tetrahydrofuran extracts a proton from the solvent to give 1,1,1-triphenylbutane much faster than it rearranges to 1,1,4-triphenylbutyllithium.

Since previous work[4] had indicated that 2,2,2-triphenylethylpotassium undergoes 1,2 migration of phenyl much more readily than the corresponding lithium compound, reaction of 4-chloro-1,1,1-triphenylbutane with molten potassium in refluxing tetrahydro-

furan was studied. The reaction was terminated by carbonation after 20 min and gave some 90% yield of neutral products and 10% of carboxylic acids. Analysis of the neutral product by gas–liquid partition chromatography (glpc) indicated that the volatile portion contained 84% of 1,1-diphenyl-1,2,3,4-tetrahydronaphthalene and 14% of 1,1,1-triphenylbutane. The structure of 1,1-diphenyl-1,2,3,4-tetrahydronaphthalene was confirmed on the purified product by melting point and spectral comparisons with an authentic sample.[7] The acidic fraction according to glpc analysis (of the methyl esters) contained small quantities of diphenylacetic acid, 2,2-diphenylpentanoic acid, triphenylacetic acid, and 2,2,5-triphenylpentanoic acid, and many unidentified acids. The present work indicates that 4,4,4-triphenylbutylpotassium (**4**) in refluxing tetrahydrofuran cyclizes to the spiro anion **2**, which ultimately yields 1,1,4-triphenylbutyl anion **5** in a yield of less than 1%; the predominant cyclization of **4** gives hydronaphthalene anion **6**, which loses hydride ion to give 1,1-diphenyl-1,2,3,4-tetrahydronaphthalene (**7**) (Scheme I). The reaction of 4-chloro-1,1,1-triphenylbutane with potassium to yield the tetrahydronaphthalene **7** is somewhat analogous to the reaction[8] of 3-methyl-3-phenyl-1-chlorobutane with potassium in refluxing cyclohexane to give a low yield of 1,1-dimethylindan (along with much 2,5-dimethyl-2,5-diphenylhexane).

SCHEME I



Since the extent of cyclization of carbanion **4** to **2** *vs.* **6** is likely to depend upon the temperature and the alkali metal, other conditions of reaction were studied. Reaction of 4-chloro-1,1,1-triphenylbutane with liquid sodium–potassium alloy in tetrahydrofuran near 0° gave some 70% yield of carboxylic acids; the volatile portion of these acids according to analysis by glpc contained some 22% of 2,2-diphenylpentanoic acid, 3.7% of triphenylacetic acid, 5.5% of 2,2,5-triphenylpentanoic acid, and three major unidentified acids. The neutral fraction contained **7**,[9] unreacted chloride, and cleavage products.

Since the reaction with sodium–potassium alloy at the lower temperature afforded increased yields of acids relative to neutral materials over that obtained with potassium metal, efforts were next extended to study the reaction of 4-chloro-1,1,1-triphenylbutane with alkali metals at still lower temperatures. In view of the fact that reactions with finely divided potassium in THF at −78° had previously proven unsuccessful[4] because of agglomeration of the potassium metal, reactions with cesium and cesium alloys seemed to offer promise. Cesium has a melting point of 28.5°; its minimum-melting solid solution[10] with potassium (49 atom % K, 51 atom % Cs) has mp −45°; its ternary eutectic[11] with sodium and potassium (11.8 atom % Na, 47.4 atom % K, 40.8 atom % Cs) has mp −79°. In a preliminary experiment 4-chloro-1,1,1-triphenylbutane was allowed to react with the theoretical quantity of cesium metal at 33 to 40° in THF for 15 min before carbonation. There was obtained some 23% yield of acids along with neutral products; the volatile acids contained 2,2,5-triphenylpentanoic acid (6%), cleavage products (43%), and unidentified acids. The volatile neutral products contained 45% of 1,1,1-triphenylbutane, 7.8% of **7**,[9] and 35% of a novel product which was ultimately shown (see later discussion) to be 9-phenyl-9-*n*-propylfluorene (**9a**). The high yield of 1,1,1-triphenylbutane as opposed to tetrahydronaphthalene **7** is of interest in comparison to the reaction with potassium.

Reaction of 4-chloro-1,1,1-triphenylbutane with excess cesium–potassium alloy at −40° gave upon carbonation some 90% yield of acids. Since the acids proved to be a complex mixture, the reaction was repeated with decomposition by methanol rather than carbon dioxide. The volatile neutral products consisted of 32% of 1,1,1-triphenylbutane, 30% of **9a**, 20% of 9-phenyl-9-*n*-propyl-2,4a,4b,7-tetrahydrofluorene (**8a**), and 8% of 1,1,4-triphenylbutane. A duplicate run in which the solution was briefly warmed to −30° before protonation gave about the same yield of 1,1,4-triphenylbutane (11%), but a higher yield (55%) of **9a**. Reaction of 4-chloro-1,1,1-triphenylbutane at −45° with the theoretical amount of Cs–K alloy for conversion of all the halide to organoalkali compound gave upon carbonation a 36:64 ratio of acids to neutral material. The volatile neutral product consisted of 93% of 1,1,1-triphenylbutane and 4% of the fluorene **9a**. This run in conjunction with the other runs with cesium suggests that 1,1,1-triphenylbutane is a major early product of the reaction of 4-chloro-1,1,1-triphenylbutane and that reaction of this hydrocarbon with excess Cs–K alloy leads to the hydrofluorene and fluorene derivatives.

The identification of 9-phenyl-9-*n*-propylfluorene and of 1,1,4-triphenylbutane from these reactions was established by isolation of the products from methanolysis and comparison with authentic samples. The authentic sample of the fluorene was prepared by alkylation[12] of the potassium salt of 9-phenylfluorene[13] with *n*-propyl bromide; the sample of 1,1,4-triphenyl-

(7) E. A. Braude, L. M. Jackman, R. P. Linstead, and G. Lowe, *J. Chem. Soc.*, 3128 (1960).

(8) H. Pines and L. Schaap, *J. Amer. Chem. Soc.*, **80**, 4378 (1958). See also G. Levin, J. Jagur-Grodzinski, and M. Szwarc, *ibid.*, **92**, 2268 (1970).

(9) Because 1,1-diphenyl-1,2,3,4-tetrahydronaphthalene and 1,1,4-triphenylbutane had the same retention time under the glpc conditions studied, this identification must remain somewhat tentative in this and other cases in which the product was not characterized as a pure substances; however, since 1,1,4-triphenylbutyl anion (like analogous anions which we have studied) is expected to be stable in tetrahydrofuran under the conditions used, we believe that the product is at least predominantly 1,1-diphenyl-1,2,3,4-tetrahydronaphthalene because it appeared with the neutral products from carbonation.

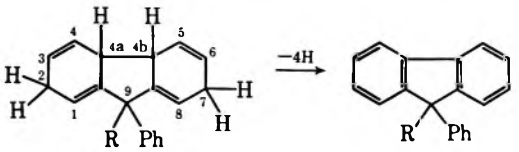
(10) C. Goria, *Gazz. Chim. Ital.*, **65**, 1226 (1935).

(11) F. Tepper, J. King, and J. Greer, "The Alkali Metals, An International Symposium Held at Nottingham on 19–22nd July, 1966," The Chemical Society, London, 1967, p 25.

(12) *Cf.* W. S. Murphy and C. R. Hauser, *J. Org. Chem.*, **31**, 85 (1966).

(13) A. Kliegel, *Chem. Ber.*, **38**, 284 (1905).

butane was similarly prepared by alkylation of diphenylmethylpotassium with 3-phenyl-1-bromopropane. The identity of the hydrofluorene **8a** rests upon



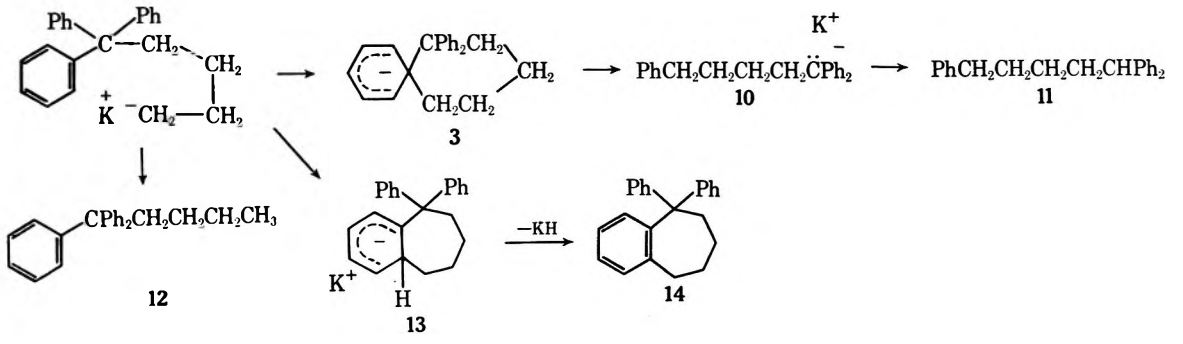
8a, R = *n*-C_3H_7
b, R = *n*-C_4H_9
c, R = CH_3

9a, R = *n*-C_3H_7
b, R = *n*-C_4H_9
c, R = CH_3

its conversion to **9a** upon dehydrogenation by sulfur in refluxing dimethylformamide, by bromine in hot *m*-dibromobenzene or simply by distillation. We believe that this compound is 9-phenyl-9-*n*-propyl-2,4a,4b,7-tetrahydrofluorene (**8a**) on the basis of our more detailed studies upon the reaction of 1,1,1-triphenylethane with Cs–K–Na alloy (see later discussion).

Reactions of 5-Chloro-1,1,1-triphenylpentane with Alkali Metals.—In view of the fact that 4-chloro-1,1,1-triphenylbutane reacted with molten potassium in THF to give a good yield of 1,1-diphenyltetrahydronaphthalene (**7**) *via* the six-membered cyclic intermediate **6** (Scheme I), it was hoped that a similar reaction of 5-chloro-1,1,1-triphenylpentane would occur (Scheme II) *via* the six-membered cyclic spiro anion **3** to give

SCHEME II



ultimately the product **11** of 1,5 migration of phenyl; the alternative ortho cyclization (to **13**) would involve formation of a seven-membered ring and hence was judged unlikely. Reaction of 5-chloro-1,1,1-triphenylpentane with potassium in refluxing THF followed by carbonation in fact gave only some 12% yield of carboxylic acids of which more than 90% were cleavage products; the predominant neutral products consisted of 60% of 1,1,1-triphenylpentane (**12**) along with mostly cleavage products. It appears that the yield of **11** and **14**, if any, did not exceed a few per cent.

The reaction of 5-chloro-1,1,1-triphenylpentane with cesium alloys was also studied. The reaction with excess Cs–K alloy at −35° and with Cs–K–Na alloy at −68° in tetrahydrofuran followed by carbonation gave, in each case, a high yield of a complex mixture of carboxylic acids. These results, along with the deep red color of the solutions, establish that a high yield of carbanions is produced under these conditions. To establish the structure of the anions, the products of decomposition by methanol were determined. The reaction with Cs–K alloy gave (according to glpc analysis) 30% of **12**, 7% of **11**, 54% of a mixture of 9-*n*-butyl-9-phenyl-2,4a,4b,7-tetrahydrofluorene (**8b**) and of 9-*n*-butyl-9-phenylfluorene (**9b**), and 9% of cleavage products.

In four runs upon 5-chloro-1,1,1-triphenylpentane with excess Cs–K–Na alloy at −68°, the products of decomposition with methanol or water were found to be 6 ± 3% of **11**, traces (3 ± 3%) of **12**, and the remainder (according to glpc analysis) a mixture of **8b** and **9b**. Since glpc analysis gave inconsistent ratios of tetrahydrofluorene to fluorene, the crude product was analyzed by nmr; this analysis showed that *all* of the fluorene derivative was present as 9-*n*-butyl-9-2,4a,-4b,7-tetrahydrofluorene, since, after correction for the known quantity of the triphenylpentanes, the ratio of aromatic to vinylic to allylic hydrogen was essentially the theoretical, 5:6:6, as expected for structure **8b**. The tetrahydrofluorene **8b** evidently dehydrogenated partially to the fluorene **9b** under our glpc conditions. This dehydrogenation also occurs on storage, especially on exposure as a thin film to light and air; most conveniently the dehydrogenation is effected by distillation *in vacuo* from a palladium–carbon catalyst at 115°. The ease of dehydrogenation agrees well with structure **8b**, since much more severe conditions are required to dehydrogenate perhydrofluorenes to fluorenes.[14] The identity of **9b** from these dehydrogenations was confirmed by isolation and comparison with an authentic sample prepared by the reaction of the potassium salt of 9-phenylfluorene with *n*-butyl bromide. While 1,1,5-triphenylpentane was not isolated in the present work, its presence was confirmed by its identity in retention time with an authentic sample on two columns upon glpc analysis.

In a further run 5-chloro-1,1,1-triphenylpentane was allowed to react at −68° with only some 2 equiv of Cs–K–Na alloy. The product from decomposition with water contained 68% of **12**, 22% of the usual fluorenes (**8b** and **9b**), and small amounts of **11** and unreacted chloride. The identity of the 1,1,1-triphenylpentane (**12**) was confirmed by isolation. This experiment suggests that **12** is the major product of initial reaction of 5-chloro-1,1,1-triphenylpentane with cesium alloy; further reaction of **12** with excess alloy evidently gives rise to the precursor of the tetrahydrofluorene derivative.

To test this postulate, **12** was allowed to react with a large excess of Cs–K–Na alloy at −60° under the usual conditions. The reaction mixture upon decomposition with methanol gave an almost quantitative yield of the

(14) F. Korte and O. Behner, *Justus Liebigs Ann. Chem.*, **621**, 51 (1959).

tetrahydrofluorene **8b**, identical in all respects with the major product from reaction of 5-chloro-1,1,1-triphenylpentane with the alloy.

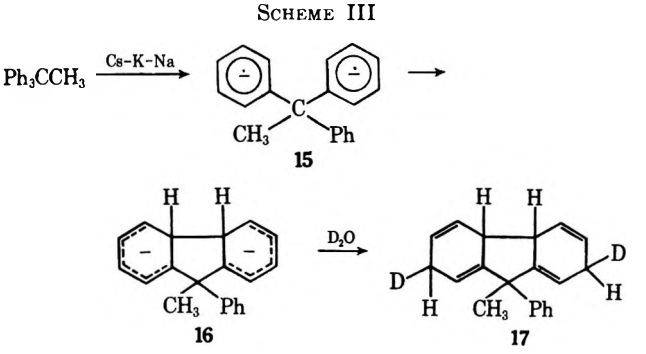
Reaction of 1,1,1-Triphenylethane with Cs–K–Na Alloy.—While the carbon skeletons of the substances previously referred to as "tetrahydrofluorenes" seem established on the basis of their ready dehydrogenation to fluorenes **9a** and **9b**, more evidence for the structures of the tetrahydrofluorenes seemed desirable. Toward this end the reaction of 1,1,1-triphenylethane with Cs–K–Na alloy was studied in some detail, since this reaction should, in terms of the previous discussion, give a simple tetrahydrofluorene **8c** which might be crystalline. In fact reaction at −70° in THF with a large excess of Cs–K–Na alloy gave the usual deep brown-red solution, which upon jetting into ice water gave an almost quantitative yield of a product, mp 96.5–97.5°, of molecular weight and analysis corresponding to the formula $C_{20}H_{20}$ as expected for 9-methyl-9-phenyl-2,4a,4b,7-tetrahydrofluorene (**8c**).

Further evidence for this structure is provided by the nmr spectrum, which shows aromatic, vinylic, allylic, and methyl hydrogens in a ratio of 5:6:6:3 as required by structure **8c**. Additional evidence is provided by the ultraviolet absorption spectrum (in ethanol) which exhibits λ_{max} 258 nm (ϵ 230) with typical benzenoid fine structure in the region of 247–268 nm and low absorbance even down to 220 nm (ϵ 643); this data shows that a benzene nucleus is present but that conjugated chromophores such as of diene or styrene type are missing. The combined nmr and uv data imply that one phenyl group is still present but that both of the other two phenyl groups of the reactant have been converted into 1,4-dihydroaromatic systems. In light of the fact that dehydrogenation under mild conditions gives 9-methyl-9-phenylfluorene (**9c**), structure **8c** is the only structure possible which is concordant with all of the data. It is obvious that structure **8c** can exist in several stereoisomeric forms. These may be classified according to whether the hydrogen atoms at 4a and 4b are cis or trans to one another; accordingly there should exist two cis isomers (both meso) and one trans-*dl* pair. It is interesting to note that evidently only one isomer is formed, in high yield, under the present reaction conditions. Indirect evidence[15] strongly suggests that this is one of the two possible cis isomers.

Decomposition of the red anion from reaction of 1,1,1-triphenylethane with Cs–K–Na alloy with D_2O gave **8c** in which 1.5 of the usual six allylic protons had been replaced by deuterium; this result implies that two protons are transferred to the anion during decomposition with protic solvents. The nmr spectrum at 100 MHz of the deuterated product showed two protons at τ 7.09 and 2.5 protons at τ 7.36, while the ordinary protium compound had two protons at τ 7.09 and four protons at τ 7.29. We assign the protons at τ 7.09 to the hydrogen atoms at 4a and 4b, while the four protons in the broad peak at τ 7.29 are assigned to the protons on C-2 and C-7. On this basis the upfield shift of 0.06 ppm in the location of the maximum for the protons on C-2 and C-7 in the deuterium compound might be attributed to a geminal deuterium isotope effect (increased shielding by D over H). This effect on proton resonances is typically 0.019 ppm toward higher magnetic field, as observed in CH_3D, but may be as high as 0.034 ppm, as in CD_3COCH_2D.[16] An alternative or additional reason for the large upfield shift may be that protonation of the red carbanion is stereospecific and that, for example, protonation occurs exclusively cis to the hydrogens at 4a and 4b; if in addition the entering protons at C-2 and C-7 absorb at somewhat lower field than the original protons, then the average center of gravity of the peak would shift upfield when D_2O was used to effect hydrolysis. Additional work is needed to confirm the postulate of stereospecific protonation and to establish conclusively the stereochemistry of the tetrahydrofluorene.

The origin of 9-methyl-9-phenyl-2,4a,4b,7-tetrahydrofluorene under the present reaction conditions is of interest. In the earlier work in which 9-*n*-propyl and 9-*n*-butyl derivatives **8a** and **8b** of the tetrahydrofluorene were formed, it was shown that the precursor of the tetrahydrofluorene was a carbanion which upon carbonation gave a high yield of a complex mixture of carboxylic acids or on protonation gave the tetrahydrofluorene. In work with 1,1,1-triphenylethane it was found that the red solution formed by stirring with excess Cs–K–Na alloy in THF at −70° upon rapid titration with a solution of *tert*-butyl alcohol in THF required 1.96 ± 0.02 molar equiv of *tert*-butyl alcohol to discharge the red color of the solution. This experiment implies that during reaction with the alloy *two* electrons are transferred to the 1,1,1-triphenylethane to form a dianion. The decomposition with D_2O, previously discussed, provides corroborative evidence, though this was less quantitative presumably because of deuterium exchange or spurious sources of acidic protons. The obvious dianion which should lead to 9-methyl-9-phenyl-2,4a,4b,7-tetrahydrofluorene-2,7-d_2 (**17**) on decomposition with D_2O is **16** (Scheme III).

SCHEME III



A plausible path to **16** is *via* two-electron transfer to 1,1,1-triphenylethane to give the diradical dianion **15**, which upon cyclization at ortho positions gives **16**. This scheme is obviously incomplete, since the role of the alkali metal cation (presumably cesium ion) is not specified. That anion **16** is red is not surprising in view

(15) Reaction of 2,2-diphenylpropane with Cs–K–Na alloy under similar conditions gives 9,9-dimethyl-2,4a,4b,7-tetrahydrofluorene, which shows nmr absorption at two slightly different locations for the two methyl groups; hence this product must have the hydrogens at 4a and 4b cis to one another since in the trans isomer the two methyl groups are in equivalent positions (unpublished work with Mr. Thomas H. Longfield).

(16) H. Batiz-Hernandez and R. A. Bernheim in "Progress in N.M.R Spectroscopy," Vol. 3, J. W. Emsley, J. Freeney, and L. H. Sutcliffe, Ed., Pergamon Press, Oxford, 1967, p 63.

of the color and spectra which have been reported[17] for some related organolithium compounds.

Scheme III is novel in that a simple phenyl radical anion is shown undergoing intramolecular cyclization with another phenyl radical anion to give a stable dianion. At first hand it is surprising that appreciable phenyl radical anion should form at all, since, in a solvent consisting of 2:1 by volume of THF and 1,2-dimethoxyethane with Na–K alloy as reducing agent, spin concentration measurements on samples 0.01 *M* in initial benzene concentration have shown that benzene radical anion concentrations at equilibrium ranged from 1 to 9 × 10^{-6} *M* over the temperature range of −20 to −83°.[18] It is possible that Cs–K–Na alloy may give a higher concentration of radical anion than Na–K. Indeed benzene has been reported[19] to form a black precipitate of unknown structure[20] when treated with cesium. Also, even though the concentration of **15** may be very low, its subsequent cyclization to **16** may drive the reaction forward. Dimerization of radical anions of pyridine, quinoline, and similar heteroaromatics is well known;[21] however, radical anions derived from aromatic hydrocarbons, such as naphthalene, anthracene, etc., are said not to dimerize because dimerization would bring about a substantial loss of resonance stability.[22] Intramolecular reactions such as **15** → **16** should, however, be more favorable than analogous intermolecular processes.

Szwarc[21] and coworkers have emphasized that radical anions of quinoline and similar substances dimerize much faster when paired with sodium cations in THF than when present as unpaired anions in hexamethylphosphoramide; association of cation and anion helps to reduce, or perhaps even avoid, repulsion between like negative charges in the dimer. We suggest that under our conditions both the formation of **15** and its dimerization to **16** are promoted by strong association between cesium (or potassium) cations and the respective anions. We note that the ionic radius of cesium (1.69 Å) is near that of a benzene ring (1.39 Å from center to the carbon atoms or 2.47 Å to the hydrogen atoms). Moreover, the cesium salt of fluorene in THF at −70° has been shown to exist essentially entirely as contact ion pairs whereas the sodium and lithium salts were completely solvent separated.[23] The reluctance of cesium cations to become solvated means that cesium ions are readily available for interaction with anions such as **15** and **16**. We suggest that the stereospecific cyclization of **15** is promoted by the presence of a cesium ion "sandwiched" between the negatively charged phenyl rings. On this basis we would predict that the hydrogen atoms at 4a and 4b in **17** should be oriented cis to one another, as appears to be the case.

(17) R. B. Bates, D. W. Gosselink, and J. A. Kaczynski, *Tetrahedron Lett.*, 199 (1967); R. Waack and M. A. Doran, *J. Amer. Chem. Soc.*, **85**, 1651 (1963).

(18) R. G. Kooser, W. V. Volland, and J. H. Freed, *J. Chem. Phys.*, **50**, 5243 (1969).

(19) L. Hackspill, *Proc. Int. Congr. Appl. Chem., 8th*, **2**, 113 (1912); *Ann. Chim. Phys. (Paris)*, **28**, 653 (1913); *Helv. Chim. Acta*, **11**, 1026 (1928); J. de Postis, *Proc. Int. Congr. Pure Appl. Chem., 11th*, **5**, 867 (1947).

(20) This product is under further investigation.

(21) J. Chaudkuri, S. Kume, J. Jagur-Grodzinski, and M. Szwarc, *J. Amer. Chem. Soc.*, **90**, 6421 (1968).

(22) M. Szwarc in "Progress in Physical Organic Chemistry," Vol. 6, A. Streitwieser and R. W. Taft, Ed., Interscience, New York, N. Y., 1968, p 399.

(23) T. E. Hogen-Esch and J. Smid, *J. Amer. Chem. Soc.*, **88**, 307, 318 (1966).

Reactions analogous to those of Scheme III are known in cases where the hypothetical cyclic dianion (analogous to **16**) or dimeric dianion is removed from the presumably dynamic but unfavorable equilibrium by loss of hydride ion, by protonation, or by protonation and further reduction. Thus benzil dianil undergoes cyclodehydrogenation with lithium in THF to produce the dianion of 9,10-dianilinophenanthrene and lithium hydride,[24] benzil is converted into phenanthrenequinone trianion radical (and KH?) by potassium in refluxing THF,[25] 1,1′-binaphthyl with lithium in THF gives perylene,[26] and tetraphenylallene with lithium gives a dibenzocycloheptatriene derivative.[27] Lithium anthracene at high concentration in diethyl ether deposits a precipitate which when hydrolyzed gives 9,9′,10,10′-tetrahydro-9,9′-dianthryl in addition to a 1:1 mixture of anthracene and 9,10-dihydroanthracene.[28] Electrolysis of phenanthrene in dimethylformamide gives 9,9′,10,10′-tetrahydro-9,9′-biphenanthrene.[29] The reaction of naphthalene with sodium in the presence of amines yields numerous products, including products of reductive dimerization.[30]

Reaction of 2-Chloro-1,1,1-triphenylethane with Cs–K–Na Alloy.—In view of the fact that 4-chloro-1,1,1-triphenylbutane and 5-chloro-1,1,1-triphenylpentane react with cesium alloys in THF at low temperature to give primarily the corresponding hydrocarbons without rearrangement of carbon skeleton when excess of alloy is avoided, it was of interest to know if 2-chloro-1,1,1-triphenylethane behaves likewise. Reaction of the latter chloride with about the theoretical amount of Cs–K–Na alloy at −65° in THF, followed by carbonation, gave some 35% yield of 2,2,3-triphenylpropanoic acid and 4.6% of 1,1,1-triphenylethane, with unreacted chloride constituting most of the remainder. Thus 2-chloro-1,1,1-triphenylethane, unlike its two higher homologs, with cesium alloy gives mostly the rearranged carbanion just as had been found previously with sodium[31] in dioxane and with potassium[4] in THF or 1,2-dimethoxyethane. The failure to obtain predominant phenyl migration in reactions of 4-chloro-1,1,1-triphenylbutane and 5-chloro-1,1,1-triphenylbutane with alkali metals under conditions where 2-chloro-1,1,1-triphenylethane gives predominantly products of phenyl migration must be ascribed to some unfavorable structural characteristics of the higher homologs.

Summary and Conclusions

Rearrangements involving 1,4 and 1,5 migration of phenyl have been observed in the present reactions of 4-chloro-1,1,1-triphenylbutane and of 5-chloro-1,1,1-triphenylpentane with cesium alloys; however, such rearrangements did not constitute more than about

(24) E. J. MacPherson and J. G. Smith, *Chem. Commun.*, 1552 (1970).

(25) N. L. Bauld, *J. Amer. Chem. Soc.*, **86**, 3894 (1964).

(26) J. J. Eisch, "The Chemistry of Organometallic Compounds, The Main Group Elements," Macmillan, New York, N. Y., 1967, p 24; M. H. Hnoosh and R. A. Zingaro, *J. Amer. Chem. Soc.*, **92**, 4388 (1970).

(27) P. Dowd, *Chem. Commun.*, 568 (1965).

(28) H. J. S. Winkler and H. Winkler, *J. Org. Chem.*, **32**, 1695 (1967).

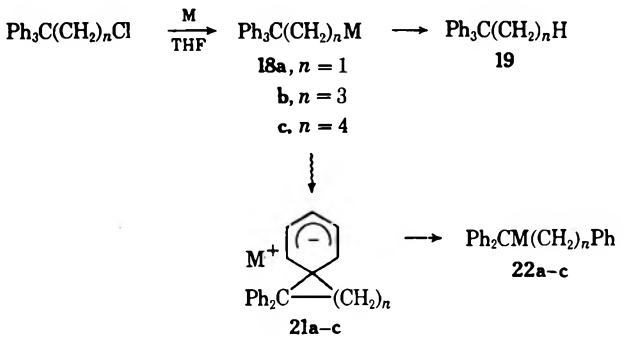
(29) S. Wawzonek and D. Wearring, *J. Amer. Chem. Soc.*, **81**, 2067 (1959).

(30) E. J. Eisenbraun, R. C. Bansal, D. V. Hertzler, W. P. Duncan, P. W. K. Flanagan, and M. C. Hamming, *J. Org. Chem.*, **35**, 1265 (1970); R. C. Bansal, E. J. Eisenbraun, and P. W. K. Flanagan, *J. Amer. Chem. Soc.*, **88**, 1837 (1966).

(31) E. Grovenstein, Jr., *J. Amer. Chem. Soc.*, **79**, 4985 (1957).

10% of the total reaction under any of the conditions studied. A more important reaction was reduction to the corresponding hydrocarbon, 1,1,1-triphenylbutane and 1,1,1-triphenylpentane, respectively. Both the rearrangement and reduction are interpreted (see Scheme IV) as proceeding by way of the same initial

SCHEME IV



unrearranged organometallic compound **18**, although only for **18a** and **18b** where M = Li has direct evidence been obtained (results of carbonation). It is at first sight surprising that **18b** and **18c** do not undergo cyclization in better yield than **18a**, since ω-aminoalkyl bromides[32] undergo cyclization considerably more readily to five-membered rings and somewhat more readily to six-membered rings than to three-membered rings.[33] In **18a**, however, the triphenylmethyl group is considerably closer to the anionic charge than in **18b** and **18c**; since this group is expected[34] to help stabilize the carbanion and should stabilize more effectively the closer to the anionic center, the order of expected stability is **18a** > **18b** ≥ **18c**. The more stable the carbanion the more slowly it should be protonated by THF to give **19** and so the more time it should possess for cyclization to **21**. Implicit in this argument is the assumption that the reaction leading to **19** is retarded more by the triphenylmethyl group than that to **21**. Another factor favoring the more ready rearrangement of **18a** than of **18b** or **18c** is that in conversion of **18a** to **21a** there is probably some relief of steric compression among the phenyl groups.[35] On the other hand, in going from **18c** to **21c**, a phenyl group and a portion of the cyclohexadienyl group are placed at axial positions on the cyclohexane ring formed on cyclization. Complications such as these are missing in cyclization of simple ω-aminoalkyl bromides which, therefore, do not serve as good models for the present system.

Liquid alloys of cesium[10,11] with potassium and sodium have apparently not been used previously in reaction with alkyl halides and hydrocarbons. These alloys permit reactions of alkali metals to be run rapidly and conveniently at low temperature; we believe, therefore, that they may find considerable application. In the present work, use of Cs–K–Na alloy has permitted the discovery that 1,2 and 1,5 migration of phenyl are rapid even at −65° in the 2,2,2-triphenylethyl and 5,5,5-triphenylpentyl anions. What may prove to be a more important discovery, and to us was unexpected, is that 1,1,1-triphenylalkanes and 1,1-diphenylalkanes[15] undergo reductive cyclization by Cs–K–Na alloy at low temperature to novel dianions of unique stereochemistry. The synthetic utility of low-temperature reductions effected by cesium alloys appears to be great and to offer exciting opportunities for future investigation.

Experimental Section[36]

Materials.—9-*n*-Butyl-9-phenylfluorene, mp 99.0–99.5° (reported[37] mp 98–99°), was prepared by reaction of the potassium salt of 9-phenylfluorene with *n*-butyl bromide in diethyl ether. Cesium metal (99.9+%) was obtained from MSA Research Corp. in sealed glass ampules. Cesium–potassium–sodium alloy was of composition (g-atom %) 47.4% K, 40.8% Cs, and 11.8% Na, corresponding to the minimum melting alloy;[11] this alloy was conveniently prepared by warming suitable proportions of the alkali metals under a nitrogen atmosphere and was stored in a tightly sealed glass-stoppered ampule under pentane. 1,1-Diphenylbutane was prepared by reaction of diphenylmethylpotassium in liquid ammonia with 1-bromopropane. 2,2-Diphenylpentanoic acid, mp 153–154° (reported[38] mp 155.5°), was made by saponification of methyl 2,2-diphenylpentanoate, which was prepared by reaction[39] of the potassium salt of methyl diphenylacetate with *n*-propyl bromide in liquid ammonia–ether solution. 1,1-Diphenyl-1,2,3,4-tetrahydronaphthalene, mp 125–126°, was obtained (25% yield) by treatment of 1,1,4-triphenylbutanol-1 with cold 92% sulfuric acid.[7] 9-Methyl-9-phenylfluorene, mp 85–87° (reported[40] mp 86–86.5°), was prepared[12,41] by metalation of 9-phenylfluorene with KNH_2 in liquid ammonia followed by reaction with an ethereal solution of methyl iodide. Methyl triphenylacetate, mp 188–189° dec (reported[42] mp 184–185°), was prepared by reaction of triphenylacetic acid with diazomethane. 9-Phenylfluorene, mp 148–150°, was prepared from triphenylcarbinol by the procedure of Kliegl.[13] 1,1,1-Triphenylbutane, mp 78–80° (reported[43] mp 79°), was prepared by reaction of *n*-propylmagnesium bromide with triphenylchloromethane in diethyl ether. 1,1,4-Triphenylbutanol-1, mp 74–75° (reported[44] mp 74–75°), was prepared by addition of 3-phenylpropyllithium to benzophenone in THF (65% yield) and by addition of 3-phenylpropylmagnesium chloride to benzophenone in diethyl ether (76% yield). 1,1,1-Triphenylethane was prepared by the procedure of Gomberg and Cone.[41,45] 1,1,1-Triphenylpentane, mp 59.5–61.0° (reported[37,46] mp 60–61°), was prepared by hydrolysis of the Grignard reagent prepared from 5-chloro-1,1,1-triphenylpentane.

General Procedure for Alkali Metal Reactions.—Reactions with alkali metals were normally conducted in a 500-ml Morton flask equipped with a Morton high-speed stirrer,[47] a condenser,

(32) G. Salomon, *Helv. Chim. Acta*, **16**, 1361 (1933); **17**, 851 (1934).

(33) For trimethylsilyl migration, however, it has been observed that 1,2 migration in silylhydrazide anions occurs more readily than 1,4 migration in etilylethylenediamine anions, while 1,4 migration in the more rigid silyl-*o*-phenylenediamine anions approaches that of silylhydrazide anions [R. West, M. Ishikawa, and S. Murai, *J. Amer. Chem. Soc.*, **90**, 727 (1968); H. F. Stewart, D. G. Koepsell, and R. West, *ibid.*, **92**, 846 (1970)].

(34) Some idea about the effectiveness of the triphenylmethyl group in stabilization of anions is provided by the relative rates (statistically corrected) of cleavage from quaternary nitrogen by sodium in liquid ammonia; for Ph_3CCH_2, $Ph_2CCH_2CH_2$, and CH_3 the relative rates are 10,000:92:1 [E. Grovenstein, Jr., and L. C. Rogers, *J. Amer. Chem. Soc.*, **86**, 854 (1964)].

(35) E. Grovenstein, Jr., and L. P. Williams, Jr., *J. Amer. Chem. Soc.*, **83**, 2537 (1961).

(36) Melting points are uncorrected. Proton magnetic resonance (nmr) spectra were obtained at 60 MHz on a Varian A-60D spectrometer and at 100 MHz on a JEOLCO 4H100 spectrometer and were taken relative to tetramethylsilane as an internal standard. Ultraviolet spectra were determined on a Cary Model 14 spectrometer and infrared spectra on a Perkin-Elmer Model 237 Infracord. Mass spectra were run on a Varian M-66 mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(37) H. Gilman and B. Gaj, *J. Amer. Chem. Soc.*, **82**, 6326 (1960).

(38) A. L. Mndzhoyan, G. T. Tatevosyan, S. G. Agbalyan, and R. K. Bostandzhyan, *Dokl. Akad. Nauk Arm. SSR*, **28**, 11 (1959).

(39) *Cf.* W. G. Kenyon, R. B. Meyer, and C. R. Hauser, *J. Org. Chem.*, **28**, 3108 (1963).

(40) P. M. G. Bavin, *Can. J. Chem.*, **38**, 882 (1960).

(41) We are indebted to Mr. Ronald H. Carter for this preparation.

(42) K. Bowden, N. B. Chapman, and J. Shorter, *J. Chem. Soc.*, 3372 (1964).

(43) M. Gomberg and L. H. Cone, *Chem. Ber.*, **39**, 2957 (1906).

(44) M. S. Kharasch and S. Weinhouse, *J. Org. Chem.*, **1**, 209 (1936).

(45) M. Gomberg and L. H. Cone, *Chem. Ber.*, **39**, 1466 (1906).

(46) J. Cason and F. J. Schmitz, *J. Org. Chem.*, **25**, 1293 (1960).

(47) A. A. Morton and L. S. Redmon, *Ind. Eng. Chem.*, **40**, 1190 (1948)

a thermometer well, and a dropping funnel. The flask was flame dried under a stream of dry nitrogen and all reactions were conducted under an atmosphere of nitrogen. For reactions of cesium and its alloys the entire apparatus was contained in a glove box under a nitrogen atmosphere in order to reduce fire hazards in working with these readily oxidizable metals. Tetrahydrofuran (THF) was stored over sodium wire and freshly distilled into the reaction flask from sodium aluminum hydride under a nitrogen atmosphere before use. In runs with liquid alkali metals, the THF was stirred with the molten metal (at 40–65°) for normally 1 hr before addition of alkyl halide; this procedure ensured both that the solvent was freed of impurities and that the alkali metal was finely divided.

4-Chloro-1,1,1-triphenylbutane.—This compound has previously been reported,[48] but without details, from reaction of triphenylmethylsodium with 1-bromo-3-chloropropane. Triphenylmethylsodium,[49] prepared from sodium amalgam (12.7 g of Na, 524 g of Hg) and triphenylchloromethane (69.7 g, 0.250 mol) in 340 ml of anhydrous ether, was siphoned under nitrogen from the mercury and added with stirring over a 10-min period to 440 ml of 1-bromo-3-chloropropane at 12 ± 3°. The red color of the triphenylmethylsodium was discharged almost immediately upon contact. The solution was filtered and the ether and excess bromochloropropane were removed finally *in vacuo* at a bath temperature of 64°. The remaining light yellow crystals (51 g, 64% yield based on triphenylchloromethane) had mp 125–170°. Recrystallization from acetone and subsequent vacuum sublimation (at a bath temperature up to 150°) gave 26.3 g of crystals, mp 129–131.5°. The analytical sample was recrystallized again from acetone to give colorless needles, mp 130.5–131.5° (reported[48] mp 130°).

Anal. Calcd for $C_{22}H_{21}Cl$: C, 82.35; H, 6.60; Cl, 11.05. Found: C, 81.92, 81.89; H, 6.59, 6.53; Cl, 11.29, 11.25.

During the purifications of the above chloride, 2.3 g of a substance of mp 164–167° and 3.6 g of a substance of mp 205–230° were obtained. In another preparation similar to the above but from 238 g of triphenylchloromethane, the product after one recrystallization from acetone amounted to 166 g (69% yield), mp 115–131°; a second recrystallization from acetone gave 120 g of 4-chloro-1,1,1-triphenylbutane, mp 129–131°.

This product was also similarly prepared by reaction of triphenylmethylsodium (from 69.7 g of triphenylchloromethane) with 400 ml of 1,3-dichloropropane. After filtration and removal of solvent and 1,3-dichloropropane *in vacuo*, oily crystals were obtained; these were washed with *n*-pentane to give 23 g (29% yield) of product, mp 122–125°. Further purification yielded a product identical (mixture melting point and ir spectral comparisons) with that from 1-chloro-3-bromopropane.

9-Phenyl-9-*n*-propylfluorene (9a).—To a solution of potassium amide, prepared from 2.86 g (0.0733 g-atom) of potassium in 200 ml of liquid ammonia, was added 1.67 g (6.89 mmol) of 9-phenylfluorene in 100 ml of diethyl ether. The brown-yellow solution was stirred at reflux for 1 hr and then 7.5 ml (0.082 mol) of *n*-propyl bromide was added. Since there was no obvious color change after 2 hr of stirring, 100 ml more of ether was added and the ammonia was allowed to evaporate. Additional *n*-propyl bromide (10 ml) was added and the solution was stirred for 2.5 hr before addition of excess ammonium chloride. The usual work-up gave 1.63 g (84% yield) of light yellow crystals which after washing with petroleum ether (bp 30–60°) amounted to 0.90 g of white solid, mp 112–115°. Two recrystallizations from ethanol gave crystals, mp 115.5–116.5°.

Anal. Calcd for $C_{22}H_{20}$: C, 92.91; H, 7.09. Found: C, 92.78; H, 7.25.

5,5,5-Triphenylpentanenitrile.—Into a flask was placed 2.00 g (6.05 mmol) of 4-chloro-1,1,1-triphenylbutane, 0.47 g (9.6 mmol) of sodium cyanide, 0.92 g (6.1 mmol) of sodium iodide, and 180 ml of dimethyl sulfoxide.[50] The flask was stoppered and stirred with a magnetic stirrer at room temperature for 10 days. After filtration the reaction mixture was poured into 100 ml of water. The solid which formed was removed by filtration, washed with 100 ml of water, and dried to give 1.80 g (95% yield) of nitrile, mp 147–149°. Two recrystallizations from acetone gave white crystals, mp 149–150°.

Anal. Calcd for $C_{23}H_{21}N$: C, 88.70; H, 6.80; N, 4.50. Found: C, 88.15; H, 6.90; N, 4.71.

5,5,5-Triphenylpentanoic Acid.—A solution of 2.86 g (9.20 mmol) of 5,5,5-triphenylpentanenitrile and 1.58 g of potassium hydroxide in 95 ml of ethylene glycol was heated at reflux for 12 hr. After the usual work-up there was obtained 2.85 g (97% yield) of white solid, mp 222–225°. The product, after recrystallization from benzene, sublimation *in vacuo* (20 μ, bath at 190°), and recrystallization from ethanol, had mp 225–227.5° dec.

Anal. Calcd for $C_{23}H_{22}O_2$: C, 83.60; H, 6.71. Found: C, 83.53; H, 6.69.

A compound, mp 222–223°, believed to be 5,5,5-triphenylpentanoic acid has been reported previously from cleavage of a substance thought to be 1,1,1,6,6,6-hexaphenylhexan-2-one by methanolic potassium hydroxide.[51]

Methyl 5,5,5-Triphenylpentanoate.—This compound, mp 97.0–97.7° (from ethanol), was prepared by reaction of the corresponding acid with diazomethane.

Anal. Calcd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02. Found: C, 83.49; H, 7.04.

2,2,5-Triphenylpentanoic Acid.—To 18.1 g (60 mmol) of 1,1,4-triphenylbutanol-1 in 85 ml of anhydrous methanol was added 0.9 ml of concentrated sulfuric acid. A precipitate rapidly formed and after 1 hr at room temperature the contents of the flask had completely solidified. The solid was recrystallized from methanol to yield,[52] after drying in air on the filter, 11.1 g (59% of 1-methoxy-1,1,4-triphenylbutane, mp 81–82°. Since a sample of this ether was found to undergo decomposition (evidently loss of methanol to give olefin) on drying *in vacuo* at room temperature, it was used without further purification or analysis. This ether, 9.73 (30.8 mmol), in 35 ml of tetrahydrofuran (THF), was added dropwise over a period of 30 min to 2.9 g (74 mg-atoms) of potassium stirred vigorously in 250 ml of THF at reflux temperature, according to our general procedure for alkali metal reactions. After 1.5 hr of additional stirring, the mixture was forced onto solid carbon dioxide. The usual work-up gave 6.7 g (68% yield) of crude acid,[53] mp 162–168°. After recrystallization from cyclohexane and then chloroform this acid had mp 168–169.5° dec.

Anal. Calcd for $C_{23}H_{22}O_2$: C, 83.60; H, 6.71. Found: C, 83.59; H, 6.58.

1,1,4-Triphenylbutane.—Diphenylmethylpotassium was prepared in 250 ml of liquid ammonia solution from reaction of 5.45 g (32.4 mmol) of diphenylmethane (in 30 ml of ether) with potassium amide (from 1.52 g, 38.9 mg-atoms, of potassium) and the red organopotassium compound was treated dropwise at reflux temperature with a solution of 1-bromo-3-phenylpropane in 30 ml of ether until the red color was discharged. Solid ammonium chloride (2.3 g) was added and the ammonia was allowed to evaporate. The residue was treated with water and extracted with ether. The ether extract yielded 7.1 g of oil which by glpc analysis contained some 84% of 1,1,4-triphenylbutane and the remainder diphenylmethane. After several distillations *in vacuo*, a sample of pure 1,1,4-triphenylbutane was obtained: $n^{27.5}D$ 1.5838; nmr (CCl_4) peaks at τ 2.89 and 2.93 (15 H, two peaks in *ca.* 2:1 ratio), 6.17 (1 H, triplet, J = 7.5 Hz), 7.43 (2 H, triplet, J = 7.2 Hz), 7.8–8.8 (4 H, multiplet). This compound is variously reported as a liquid,[54] $n^{20}D$ 1.5993, and a solid,[55] mp 78–79°; attempts to obtain a crystalline product were unsuccessful in our hands.

Anal. Calcd for $C_{22}H_{22}$: C, 92.26; H, 7.74. Found: C, 92.27; H, 7.72.

Reaction of 4-Chloro-1,1,1-triphenylbutane with Lithium.—In the usual apparatus was placed 250 ml of THF, 0.63 g (0.090 g-atom) of finely cut lithium wire (from Lithium Corp. of America, 0.05% Na max), and 0.15 ml of methyl iodide. The reaction flask was cooled to −5 ± 5, some 5% of a solution of 4-chloro-1,1,1-triphenylbutane (4.0 g, 12 mmol) in 20 ml of THF was added, and vigorous stirring was continued for 2 hr. An additional 0.1 ml of methyl iodide and 5% of the chloride solution was then added and stirring was continued for 1.5 hr, by which time the color of the solution was orange. The solution was then cooled to −55 ± 5°, the remainder of the chloride was added

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(49) W. B. Renfrow, Jr., and C. R. Hauser in "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 607.

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(51) F. J. Piehl and W. G. Brown, *ibid.*, **75**, 5025 (1953).

(52) *Cf.* K. Ziegler, K. Richter, and B. Schnell, *Justus Liebigs Ann. Chem.*, **443**, 177 (1925).

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(54) A. D. Petrov and V. M. Vdovin, *Zh. Obshch. Khim.*, **27**, 45 (1957).

(55) F. Bergmann, S. Israelashvili, and D. Gottlieb, *J. Chem. Soc.*, 2522 (1952).

dropwise, and stirring was continued for 3 hr before the solution was forced onto solid crushed carbon dioxide. The next day some of the unreacted lithium metal was removed, 200 ml of water was added (to decompose the remaining lithium), and the THF was removed *in vacuo* on a steam bath. The aqueous residue was acidified with 10% sulfuric acid and extracted well with ether. The ethereal phase was extracted with dilute sodium hydroxide. The ether phase yielded 3.0 g of neutral material. The alkaline solution was acidified with 10% sulfuric acid and extracted with ether. The ether extract, after drying over anhydrous $MgSO_4$, yielded 1.2 g of crude acid,[56] mp 180–230°. One recrystallization from benzene gave 0.86 g of acid, mp 222–225° dec. Two more recrystallizations from benzene gave material, mp 223–224° dec, which gave no mixture melting point depression with authentic 5,5,5-triphenylpentanoic acid (prepared *via* the nitrile).

In another run after the usual initiation at −5°, 7.53 g (23.5 mmol) of 4-chloro-1,1,1-triphenylbutane was allowed to react with 0.51 g of lithium in 250 ml of THF with vigorous stirring at −60 ± 5° for 3.5 hr. The reaction mixture was then stirred at 0 ± 3° for 2 hr before carbonation. The usual work-up yielded 1.28 g of acid, mp 207–220°. One recrystallization from benzene gave 0.50 g of acid, mp 217–223°; a mixture melting point of this acid with the 5,5,5-triphenylpentanoic acid obtained in the previous run was not depressed.

In a final run after the usual initiation at −5°,4-chloro-1,1,1-triphenylbutane (10.0 g, 31.1 mmol) was allowed to react with 0.64 g (92 mg-atoms) of lithium in 250 ml of THF at −60° for 4 hr. The reaction mixture was then stirred at 25 ± 2° for 2 hr before carbonation. The usual work-up gave 9.1 g of neutral material and 0.37 g of acidic material. The acids were methylated with diazomethane before analysis by gas–liquid partition chromatography[57] (glpc). There was obtained (as methyl esters) 46% of 5,5,5-triphenylpentanoic acid, 17% of a likely isomeric acid at 0.81 times the retention time of 5,5,5-triphenylpentanoic acid, and seven acids of lower molecular weight (products of pyrolysis or fragmentation); none of the methyl ester of 2,2,5-triphenylpentanoic acid could be detected. Analysis (glpc) of the neutral material gave 87% of 1,1,1-triphenylbutane, 3% of a substance of 34% longer retention time (likely[9] 1,1-diphenyltetrahydronaphthalene), and 10% of 4-chloro-1,1,1-triphenylbutane. A sample (2.0 g) of the neutral material was distilled in a sublimation apparatus at 0.01 mm and 103° to give 1.2 g of white solid, mp 55–74°. Two recrystallizations from ethanol gave 0.47 g of compound, mp 77–79°, which was identified as 1,1,1-triphenylbutane by comparisons of melting point, mixture melting point, and ir spectra with those of an authentic sample.[43]

Reaction of 4-Chloro-1,1,1-triphenylbutane with Potassium.—In the usual apparatus was placed 250 ml of THF and 3.44 g (0.088 g-atom) of freshly cut potassium. The mixture was heated at reflux with vigorous stirring for 50 min and then a solution of 10.08 g (31.4 mmol) of 4-chloro-1,1,1-triphenylbutane in 70 ml of THF was added over a period of 10 min. On addition of the first portion of halide the solution turned a deep red; the final color was like that of bromine. After cooling to room temperature in 10 min, the mixture was forced onto a large excess of solid carbon dioxide. A 300-ml portion of absolute ethanol was added to destroy any unreacted potassium. The next day, solvents were largely removed *in vacuo*, water was added to the residual viscous liquid, and the mixture was extracted with three 200-ml portions of ether. The ether extract, after drying over anhydrous $MgSO_4$, yielded 9.5 g of crude, semisolid neutral material. The aqueous layer, after acidification with 10% hydrochloric acid and extraction by ether, yielded 1.08 g of oily acids. Analysis of the neutral fraction by glpc[57] showed the presence of 84% of 1,1-diphenyl-1,2,3,4-tetrahydronaphthalene (**7**), 14% of 1,1,1-triphenylbutane, and 0.8 and 0.4% of two cleavage products (apparently 1,1-diphenylbutane and triphenylmethane, respectively). Analysis (glpc) of the methyl esters of the acids at 284° gave the following products, listed as area per cent (relative retention time, identity of acid): 0.8 (0.38, diphenylacetic acid); 4.5 (0.52, 2,2-diphenylpentanoic acid), 47 (0.58), 5 (0.67), 2.7 (1.00, triphenylacetic acid), 1 (1.62), 5.7 (1.79, 2,2,5-triphenylpentanoic acid), 28 (2.10), and 5 (2.96). A sample of 7.3 g of the neutral material was sublimed at 0.3 mm at a bath temperature of 102° to give 3.7 g of white solid, mp 80–115°. Recrystallization of 1.89 g of this product from ethanol gave 1.11 g (indicative of 32% yield based on chloride) of product, mp 125–126°; this compound is identified as **7** based on melting point, mixture melting point, and ir spectral comparisons with an authentic sample.[7] The nmr spectrum provided confirmatory evidence: nmr ($CDCl_3$) τ 2.8–3.5 (14 H, complex multiplet), 7.3 (4 H, overlapping triplets), and 8.3 (2 H, complex multiplet). A repetition of this run but with a total reaction time of 1.7 hr at reflux temperature gave 7 g of a very complex mixture of acids.

Reaction of 4-Chloro-1,1,1-triphenylbutane with Sodium–Potassium Alloy.—To sodium–potassium alloy, prepared from 10.3 g (0.26 g-atom) of potassium and 3.1 g (0.13 g-atom) of sodium in 250 ml of THF, was added 10.0 g (31.1 mmol) of 4-chloro-1,1,1-triphenylbutane in 70 ml of THF over a period of 40 min while the solution was stirred vigorously with cooling by an ice bath (0°). The red mixture was stirred for an additional 1 hr at ice-bath temperature before carbonation. The usual work-up gave 3.0 g of neutral material and the remainder acids (*ca.* 7 g). Analysis[57] of the neutral material by glpc showed the presence of 15% of 4-chloro-1,1,1-triphenylbutane, 32% of **7**,[9] a trace of 1,1,1-triphenylbutane, and the remainder some five cleavage products of which only triphenylmethane (3%) was identified. Analysis of the methyl esters of the acids by glpc at 284° gave the following products, listed as area per cent (relative retention time, identity): 22 (0.52, 2,2-diphenylpentanoic acid), 38 (0.58), 16 (0.67), 3.7 (1.00, triphenylacetic acid), 5.5 (1.79, 2,2,5-triphenylpentanoic acid), 12 (2.10).

Reaction of 4-Chloro-1,1,1-triphenylbutane with Cesium.—In the usual apparatus was placed 4.09 g (0.0308 g-atom) of cesium metal and 250 ml of THF. Upon stirring the solution developed a pale blue color. After stirring for 35 min at 40 ± 5°, 5.01 g (15.6 mmol) of 4-chloro-1,1,1-triphenylbutane was dusted into the reaction mixture over a period of 4 min at 33°. A dark red color rapidly developed in the solution. Stirring was continued for 11 min more at 40° before carbonation. The usual work-up gave 1.22 g of acids and 4.0 g of crude neutral product. Analysis[57] of the methyl esters of the acids by glpc at 284° gave the following products, listed as area per cent (relative retention time, identity): 1.6 (0.38, diphenylacetic acid), 6.5 (0.52, 2,2-diphenylpentanoic acid), 3 (0.67), 4.8 (1.00, triphenylacetic acid), 26 (1.54), 6.1 (1.79, 2,2,5-triphenylpentanoic acid), 35 (2.1), 16 (2.8). Analysis of the neutral material by glpc at 274° gave (listed as before): 6.7 (0.21), 5.1 (0.40), 45 (1.00, 1,1,1-triphenylbutane), 35 (1.05, **9a**), and 7.8 (1.33, **7**[9]).

Reaction of 4-Chloro-1,1,1-triphenylbutane with Cesium–Potassium Alloy.—In a run with 1.16 g (0.0297 g-atom) of potassium and 3.93 g (0.0296 g-atom) of cesium in 250 ml of THF, 4.45 g (13.9 mmol) of 4-chloro-1,1,1-triphenylbutane in 50 ml of THF was added dropwise at −25° over a period of 30 min and stirring was continued for 34 min before carbonation. There was isolated 4.1 g of a complex mixture of acids, mp 70–160°. The acids were converted to their methyl esters with diazomethane; some 48% of these esters were volatile in a preparative glpc separation. The volatile esters *via* glpc analysis consisted of 10.8% of methyl triphenylacetate, 14% of methyl 2,2,5-triphenylpentanoate, and the remainder of seven unidentified esters. Methyl triphenylacetate was isolated as crystals, mp 187–189°, and was shown to be identical (melting point, mixture melting point, nmr spectrum) with an authentic sample. Methyl 2,2,5-triphenylpentanoate, however, was not isolated as a pure substance. A repetition of this run at a temperature of −40 ± 5° with 5.9 g of 4-chloro-1,1,1-triphenylbutane (5.9 g of Cs, 1.5 g of K) gave 5.5 g of acids; glpc analysis[57] of the methyl esters at 275° gave the following products, listed as area per cent (relative retention time, identity): 3 (0.40, 2,2-diphenylpentanoic acid?), 13.8 (1.00, triphenylacetic acid), 1.2 (1.70), 27.6 (2.14, 2,2,5-triphenylpentanoate acid), 32 (2.60), 5.5 (2.90), 1.8 (3.2), 1.1 (3.6), 1.1 (4.0), 3.9 (4.6), 1.1 (5.2), and 6.8 (6.1).

In another run 12.56 g (39.2 mmol) of 4-chloro-1,1,1-triphenylbutane in 50 ml of THF was added dropwise over a period of 20 min to 5.54 g (0.0416 g-atom) of cesium and 1.45 g (0.0371 g-atom) of potassium stirred vigorously in 250 ml of THF at −45 ± 5°. Stirring was continued for 30 min more before carbonation.

(56) This yield may be low because the reaction flask was not flame-dried.

(57) The analyses were ordinarily run at about 280° on an F & M Scientific Co. Model 810 chromatograph equipped with flame ionization detectors with 6 ft × 0.25 in. columns packed with 10% silicone gum rubber (SE-30) on 60–80 mesh Chromosorb G (acid washed and silanized with dimethyldichlorosilane). The analyses are reported as area per cent of total volatile constituents; therefore, while these analyses should indicate the correct relative amounts of isomers, including compounds differing only in the number of hydrogen atoms, the analyses are ordinarily only of semiquantitative significance.

The usual work-up gave 4.4 g of acids and 7.8 g of neutral product. Analysis[57] of the neutral product by glpc showed that the volatile portion consisted of 93% of 1,1,1-triphenylbutane, 3.8% of **9a**, and 3.0% of **7**.[9] A quantitative glpc analysis showed that the neutral product contained 3.7 g (33% absolute yield based on starting chloride) of 1,1,1-triphenylbutane. The acid fraction consisted of the usual complex mixture; methyl 2,2,5-triphenylpentanoate constituted 8.5 area % of the volatile esters, although the absolute yield was only 1.4% (based on starting chloride). Only about half of both the methyl esters and neutral products were glpc volatile in this run.

In another run, 6.12 g (19.1 mmol) of 4-chloro-1,1,1-triphenylbutane in 40 ml of THF was added over a period of 18 min to 5.72 g (0.0431 g-atom) of cesium and 1.47 g (0.0376 g-atom) of potassium (as Cs–K alloy) stirred in 250 ml of THF at −42 ± 2°. Stirring was continued at the same temperature for 40 min before addition of 50 ml of methanol to the red solution. The usual work-up gave 5.6 g of crude product; analysis[57] by glpc at 250° showed the presence of the following substances, listed as area per cent (retention time in minutes, identity): 4.2 (1.9–9.2, six unknown products), 32 (10.5, 1,1,1-triphenylbutane), 30 (10.9, **9a**), 20 (11.5, **8a**) and 8 (11.8, 1,1,4-triphenylbutane). A 0.257-g portion of the crude product was heated with 0.029 g of sulfur in 15 ml of *N*,*N*-dimethylformamide at reflux for 5.5 hr. After washing with water, the organic fraction was evaporated to give 0.195 g of brown tar. Analysis of this tar by glpc showed that **8a** had disappeared while **9a** had increased in amount relative to the other components. In another dehydrogenation procedure,[58] to 0.209 g of the crude product in 10 ml of *m*-dibromobenzene at 215° was added dropwise over 5 min 0.16 ml of 2.5% (by volume) bromine in *m*-dibromobenzene and the mixture was heated at 215° for 2.5 hr. Analysis by glpc showed again that the tetrahydrofluorene had disappeared and more **9a** had appeared. A similar dehydrogenation was run on another 0.103 g of the crude product. The two bromination products were combined; solvent was removed *in vacuo*; and the residue was combined with 0.186 g of the product from the sulfur treatment. The mixture was distilled in a sublimation apparatus at 100° and 50 μ to give 0.206 g of semisolid product. Recrystallization of 0.152 g of this product from ethanol gave 0.036 g of crystals, mp 113–114°; another recrystallization from ethanol gave a pure product, mp 115.3–116.0° (9-phenyl-9-*n*-propylfluorene, **9a**).

In a final run 6.65 g (20.7 mmol) of 4-chloro-1,1,1-triphenylbutane in 30 ml of THF was added over a 25-min period to Cs–K alloy prepared from 6.39 g (0.0480 g-atom) of cesium and 1.61 g (0.0411 g-atom) of potassium in 250 ml of THF at −45° in the usual manner, except that *ca.* 10% of the halide was prematurely added to the flask at room temperature before refluxing the solvent with alkali metal. The reaction mixture was then stirred at −45 ± 3° for 30 min, allowed to warm to −30°, and then forced into 110 ml of methanol at −55°. The mixture was neutralized with 5% hydrochloric acid. The usual work-up gave 4.95 g of a colorless oil (another 1.54 g of product was recovered from the reaction flask). Analysis[57] of this oil by glpc at 250° gave the following results, listed as area per cent (retention time in minutes, identity): 8.9 (1.9–7.4, four unknown compounds), 9.5 (10.5, 1,1,1-triphenylbutane), 55 (10.9, **9a**), 15 (11.5, **8a**), 11 (11.8, 1,1,4-triphenylbutane). Since other work indicated that the tetrahydrofluorene derivative was generally converted to the fluorene on distillation *in vacuo*, a portion (3.44 g) of the colorless oil was distilled at 100° and 10 μ to give 2.69 g of semisolid product. One recrystallization of 1.90 g of this material from ethanol gave 0.84 g of crystals, mp 108–114°, and mother liquor A. Sublimation of 0.174 g of these crystals at 100° and 10 μ and recrystallization from ethanol gave 0.132 g of white crystals, mp 113–115°; after another recrystallization from ethanol the melting point was 115.0–115.8°.

Anal. Calcd for $C_{22}H_{20}$: C, 92.91; H, 7.09; mol wt, 284. Found: C, 93.37; H, 6.76; mol wt (mass spectrum[59]), 284.

The compound of mp 115–116° gave nmr absorption (CCl_4) at τ 2.2–3.0 (13 H, complex multiplet), 7.63 (2 H, triplet, J = 7 Hz), 9.28 (5 H, complex multiplet); λ_{max}^{EtOH} 266 nm (ε 14,300), 294 (5310), 306 (8900). This compound was found to be identical with the synthetic sample of 9-phenyl-9-*n*-propylfluorene (prepared from 9-phenylfluorene) on the basis of melting point, mixture melting point, ir, and uv spectral comparisons.

The mother liquor A above was evaporated on a steam bath and the residue was distilled at 20 μ. A 0.285-g portion of the distillate was subjected to liquid phase chromatography on 80 g of silica gel (E. Merck A.-G., Darmstadt, Germany, No. 7734) in a 2.0 × 60 cm column. Elution with petroleum ether gave fractions 3 and 4 (0.15 g), which consisted of a 2:1 mixture of **9a** and 1,1,1-triphenylbutane, and fractions 8 and 9 (0.050 g), which contained some 90% of 1,1,4-triphenylbutane. The identity of fraction 8 was confirmed, after distillation *in vacuo*, by ir and nmr spectral comparisons with the synthetic sample of 1,1,4-triphenylbutane (prepared from diphenylmethane).

5-Chloro-1,1,1-triphenylpentane.—This compound was prepared[60] by a procedure analogous to that used for 4-chloro-1,1,1-triphenylbutane except that triphenylmethylsodium (from 278.8 g of triphenylchloromethane) in 1250 ml of diethyl ether was added slowly over a period of 2 hr under nitrogen to 500 ml of 1,4-dichlorobutane stirred in a 3-l. Morton flask cooled to −40°. After the usual work-up, the oily product was crystallized from petroleum ether to give 161 g (48% yield) of crude crystals, mp 65–73°. Several recrystallizations from acetone gave 84.5 g of white crystals, mp 75–78°; after further recrystallization the most highly purified sample had mp 79.0–79.6°.

Anal. Calcd for $C_{23}H_{23}Cl$: C, 82.49; H, 6.92; Cl, 10.60. Found: C, 82.55; H, 7.12; Cl, 10.14.

6,6,6-Triphenylhexanenitrile.—Into a flask was placed 3.34 g (10.0 mmol) of 5-chloro-1,1,1-triphenylpentane, 0.90 g (18 mmol) of sodium cyanide, 1.75 g (12 mmol) of sodium iodide, and 250 ml of dimethyl sulfoxide. The flask was stoppered and stirred at room temperature for 12 days. The work-up was like that for 5,5,5-triphenylpentanenitrile. There was obtained 2.95 g (91% yield) of nitrile, mp 84.5–86°. After two recrystallizations from acetone and sublimation *in vacuo*, the product had mp 85.5–86.5°.

Anal. Calcd for $C_{24}H_{23}N$: C, 88.57; H, 7.12; N, 4.30. Found: C, 88.48; H, 7.20; N, 4.34.

6,6,6-Triphenylhexanoic Acid.—A solution of 1.55 g (4.8 mmol) of 6,6,6-triphenylhexanenitrile and 0.91 g of potassium hydroxide in 40 ml of ethylene glycol was heated at reflux for 9 hr. The usual work-up gave 1.50 g (91% yield) of white crystals, mp 140–142°. Two recrystallizations from benzene yielded product, mp 141.5–142.0°. The analytical sample was sublimed twice *in vacuo* (final mp, 141.8–142.7°).

Anal. Calcd for $C_{24}H_{24}O_2$: C, 83.68; H, 7.02. Found: C, 83.60; H, 7.03.

1,1,5-Triphenylpentanol-1.—To the Grignard reagent prepared from 40.2 g (0.238 mol of 4-phenyl-1-chlorobutane and 6.8 g (0.28 g-atom) of magnesium in 130 ml of diethyl ether was added 30.9 g (0.170 mol) of benzophenone in 125 ml of ether. The solution was stirred at reflux for 3 hr and then decomposed with 150 ml of saturated ammonium chloride solution. The solution was extracted with ether; the ether extract was washed with 5% $NaHCO_3$ and dried over anhydrous $MgSO_4$. After removal of ether, the residue was washed with hexane to give 25 g of crude crystals, mp 54–64°. Recrystallization of 14.3 g of this product from ethanol gave 5.7 g, mp 78–86°. Recrystallization further from ligroin (bp 90–120°), with discarding of the first crystals which separated and contained benzpinacol, and then recrystallization from carbon tetrachloride followed by petroleum ether gave 2.2 g of alcohol, mp 84.5–86.0°.

Anal. Calcd for $C_{23}H_{24}O$: C, 87.28; H, 7.65. Found: C, 87.06; H, 7.64.

1,1,5-Triphenylpentane (11).—To 2.0 g (6.3 mmol) of 1,1,5-triphenylpentanol-1 in 15 ml of anhydrous methanol was added four drops of concentrated sulfuric acid; after some 15 min the entire mass solidified and was stored overnight at 0°. The precipitate was washed with cold methanol and after drying in a desiccator over KOH amounted to 1.24 g of product: mp 61–63°; nmr (CCl_4) peaks at τ 2.80 and 2.93 (15 H, two peaks in *ca.* 2:1 ratio), 7.03 (3 H, singlet, CH_3O), 7.3–9.2 (8 H). Since this ether appears to be unstable on storage, it was used the next day. In the general apparatus for alkali metal reactions was placed 200 ml of THF and 0.52 g (0.013 g-atom) of potassium and the mixture was stirred at reflux for 1 hr. A solution of 1.18 g (3.6 mmol) of the methyl ether in 10 ml of THF was added over a period of 10 min. The solution developed an orange color which

(58) *Cf.* O. W. Webster and W. H. Sharkey, *J. Org. Chem.*, **27**, 3354 (1962).

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deepened to orange-red. Stirring at reflux was continued for 35 min longer and then methanol (10 ml) was added. Most of the solvent was then removed on a rotating evaporator, water was added, and the mixture was extracted with ether. After removal of ether, the residue was distilled *in vacuo* and purified by chromatography on 100 g of silica gel (E. Merck A.-G., Darmstadt, Germany, No. 7734) with elution by petroleum ether. There was separated 0.60 g of an oil which solidified on storage at 0°: mp 37.0–38.0; nmr (CCl_4) peaks at τ 2.89 and 2.93 (15 H, two peaks in *ca.* 2:1 ratio), 6.20 (1 H, triplet), 7.49 (2 H), 7.7–9.0 (complex multiplet). The analytical sample was redistilled *in vacuo*.

Anal. Calcd for $C_{23}H_{24}$: C, 91.95; H, 8.05. Found: C, 91.83; H, 8.08.

Reaction of 5-Chloro-1,1,1-triphenylpentane with Potassium.—In the usual apparatus was placed 230 ml of THF and 2.10 g (0.0536 g-atom) of potassium; the mixture was heated at reflux with vigorous stirring for 30 min. A solution of 5.98 g (17.8 mmol) of 5-chloro-1,1,1-triphenylpentane in 40 ml of THF was then added dropwise over a period of 20 min. The solution was allowed to cool to room temperature over a period of 20 min with continued stirring before carbonation of the deep red colored solution. The usual work-up gave 0.64 g of acids and 4.69 g of neutral material. Analysis[57] of the methyl esters of the acids by glpc at 295° showed the presence of the following substances, listed as area per cent (retention time relative to methyl 6,6,6-triphenylhexanoate): 1 (0.29), 6 (0.32), 67 (0.35), 8 (0.48), 2 (0.67), 3 (0.77), and 3 (1.1). Analysis of the neutral material by glpc at 250° gave the products, listed as area per cent (relative retention time): 1.1 (0.29), 18 (0.39), 7.5 (0.63), 11 (0.73), 60 (1.00, 1,1,1-triphenylpentane, **12**), 1.7 (1.4). A portion (2.24 g) of the neutral material was chromatographed on 180 g of neutral aluminum oxide (Merck, reagent grade) with elution by petroleum ether–benzene; there was separated 0.41 g of product, mp 59–60°, and another 0.26 g, mp 56–60°. This product was identified as **12** on the basis of melting point and mixture melting point comparisons with the hydrocarbon prepared by hydrolysis of the Grignard reagent from 5-chloro-1,1,1-triphenylpentane.

Reaction of 5-Chloro-1,1,1-triphenylpentane with Cs–K Alloy.—In the usual apparatus were placed 4.20 g (0.0316 g-atom) of cesium and 1.14 g (0.0292 g-atom) of potassium in 250 ml of THF. The solution was stirred at reflux temperature for 30 min and then cooled to $-35 \pm 2°$. To the deep blue solution was added 5-chloro-1,1,1-triphenylpentane (4.53 g, 13.1 mmol) in 30 ml of THF over a period of 30 min; the solution developed a deep red-brown color like that of bromine and was stirred at $-35°$ for an additional 30 min. Some 60% of the solution was then forced onto solid carbon dioxide and to the remainder in the flask was added 10 ml of methanol over a period of several minutes. After the usual work-up the carbonated portion yielded 2.2 g of acids and 0.16 g of neutral material. According to glpc analysis[57] of the methyl esters, the acids consisted of some 14 components, seven of which, constituting 90 area per cent of the total, were of a molecular weight near that of the starting chloride, while the remainder were cleavage products. The neutral material from the carbonation consisted of some 83% of **12** containing a small quantity, evidently, of **9b**. The product from the decomposition with methanol amounted to 1.7 g. According to glpc at 245° this consisted primarily of four components, listed as area per cent (retention time in minutes, identity): 30 (9.2, **12**), 19 (9.8, **9b**), 35 (11.4, **8b**), 6.7 (13.2, **11**), along with some 9% of cleavage products of which that of longest retention time (4.6 min) was evidently triphenylmethane (*ca.* 1%). The nmr spectrum of this mixture of hydrocarbons (in CCl_4) had characteristic absorption (complex multiplets) at τ 2.87 (aromatic H), 4.28 (vinyl H), and 7.28 (allylic H) in a ratio of 2.2:1.0:1.0; the high ratio of vinyl to aromatic hydrogen suggests that the fluorene **9b**, found on glpc analysis, was present in the original reaction mixture as the corresponding tetrahydrofluorene **8b**. We have found that, whereas crude **8b** can sometimes be distilled at 0.1 mm at a bath temperature of 110° without dehydrogenation, yet on standing for 5 days at room temperature in an open evaporating dish some half of the tetrahydrofluorene was dehydrogenated (oxidized?) to **9b**; after 4 more days this dehydrogenation was nearly complete. A portion of the product from decomposition with methanol was subjected to chromatographic separation on silica gel (elution with pentane–benzene); a fraction, which according to glpc was a 50:50 mixture of **12** and **9b**, absorbed at λ_{max}^{EtOH} 266, 294, and 306 nm, just as found, but at essentially half the intensity, for **9a**.

A repetition of this run, but after addition of 5-chloro-1,1,1-triphenylpentane with stirring for 1 hr at 0° (rather than 30 min at −35°), gave upon carbonation a 39:61 (by weight) of neutral products to acids. Some 90% of both the acids and neutral products were products in which one or more of the C–C bonds of the original 1,1,1-triphenylpentane derivative had been cleaved.

Reaction of 5-Chloro-1,1,1-triphenylpentane with Cs–K–Na Alloy.—In the usual apparatus was placed 4.83 g (0.0363 g-atom) of cesium, 1.59 g (0.041 g-atom) of potassium, and 0.20 g (0.0087 g-atom) of sodium in 250 ml of THF. The mixture was stirred vigorously at reflux for 1 hr, then cooled to $-68 \pm 2°$, and held at this temperature while 4.48 g (14.4 mmol) of 5-chloro-1,1,1-triphenylpentane in 30 ml of THF was added over a 30-min period. Stirring was continued for an additional 30 min; then 10% of the brown-red solution was forced onto solid carbon dioxide; and to the remainde rin the Morton flask was added rapidly, through a dropping funnel, 250 ml of methanol. The usual work-up of the carbonated portion gave, after esterification with diazomethane, 0.50 g of methyl esters and 0.08 g of neutral material. Analysis[57] of these by glpc at 255° gave products listed as area per cent (retention time in minutes, identity): for the esters, 6 (3.6 and 3.9), 43 (6.4), 17 (7.4), 17 (11.3), and 17 (14.2); for the neutral material, >90 (6.3, **12**), trace (6.9, **9b**). The neutral product from decomposition with methanol amounted to 3.71 g; analysis by glpc at 255° gave (similarly listed): ~3 (6.3, **12**), 17 (6.9, **9b**), 75 (7.8, **8b**), and 5 (9.0, **11**). An nmr analysis (CCl_4) upon the crude product from methanol decomposition gave characteristic peaks at τ 2.84 (aromatic H), 4.25 (vinyl H), and 7.25 (allylic H) in a ratio of 1.10:1.00:0.94. The glpc analysis, however, leads to a ratio of aromatic to vinyl hydrogens of 1.59; evidently all of the fluorene **9b** is contained in the original product as the tetrahydrofluorene **8b**, but the latter dehydrogenates in part under glpc conditions. If this assumption is correct, the predicted ratio of aromatic to vinyl hydrogen is 1.05 (essentially that found). Storage of the CCl_4 solution used for nmr analysis for 53 days at 5°, followed by repeated nmr analysis, gave the original peaks now in a ratio of 1.80:1.00:1.07 for aromatic, vinyl, and allylic hydrogen, respectively. The neutral product (3.7 g) was chromatographed on 300 g of neutral alumina (Merck) with elution by petroleum ether–benzene; there was obtained some 1.5 g of a mixture of the fluorene and the tetrahydrofluorene. A midcut of this (0.41 g) was intimately mixed with 0.10 g of 10% Pd on carbon catalyst, put into a sublimation apparatus, and heated at 90–110° at 0.01 mm for 8 hr. There was sublimed 0.28 g of product, mp 88–90°; recrystallization from ethanol gave 0.12 g, which after vacuum sublimation had mp 97.5–98.0°. This compound was found to be identical with an authentic sample of 9-*n*-butyl-9-phenylfluorene according to mixture melting point and ir spectral comparisons; the uv spectrum was identical with that of **9a**.

In four runs similar to that described above (in one of these the reaction mixture was jetted into 1200 ml of ice water rather than decomposed with methanol) the average yield (glpc) of **11** was $6 \pm 3\%$, that of **12** was $3 \pm 3\%$, and the remainder was, according to nmr analysis, primarily **8b**, although glpc analysis again showed variable quantities of **9b**. The yield of hydrocarbons was quantitative in these runs. Distillation at a bath temperature of 100° and a pressure of 0.1 mm showed that at least 84% of the hydrocarbon was volatile; this distillation sometimes, but not always, converted tetrahydrofluorene partially to fluorene according to nmr analysis. For complete conversion of tetrahydrofluorene to fluorene, the best procedure found was to heat (115°) with and ultimately distil *in vacuo* from 5% Pd/C catalyst (see above); this procedure converted some 80% of the volatile hydrocarbon mixture to **9b** according to nmr analysis (based on the characteristic peaks of the fluorene at τ 2.31 and 2.38 and the common peak for all aromatics near 2.9). The identity of the 1,1,5-triphenylpentane in these runs rests on its identity in retention time with an authentic sample in glpc analysis on two columns (silicone gum rubber on Chromosorb G and Apiezon L on Chromosorb P).

In a further run 5-chloro-1,1,1-triphenylpentane (3.00 g, 9.0 mmol) was allowed to react, exactly according to the previous procedure, with 1.5 g (0.019 ± 0.002 g-atom) of Cs–K–Na alloy. The reaction was terminated by forcing the reaction mixture into a large excess of ice water. After extraction with ether, the ethereal extract was dried over anhydrous $MgSO_4$ and then P_2O_5. Analysis by glpc indicated the presence of **12** (68%), **9b** (22%), **11** (3%), and 5-chloro-1,1,1-triphenylpentane (6%). After distillation *in vacuo*, analysis by nmr indicated the presence of 6% **8b** and 13% **9b** in the distillate. Chromatography of 0.97 g of the

distillate on 150 g of neutral alumina (Merck) with elution by petroleum ether–benzene gave, after repeated chromatography of mixtures obtained from the first chromatograph, 0.41 g of **12** (mp 58–60°), whose identity was established by mixture melting point, ir, and nmr spectral comparisons with an authentic sample, and 0.10 g of **9b** (95% pure by glpc), whose identity was confirmed by ir spectral comparison with an authentic sample.

Reaction of 1,1,1-Triphenylpentane with Cs–K–Na Alloy.—To 1.47 g (0.0194 g-atom) of Cs–K–Na alloy in 250 ml of THF at $-60 \pm 3°$ was added over a 3-min period 0.281 g (0.935 mmol) of 1,1,1-triphenylpentane in 5 ml of THF; vigorous stirring was continued for 57 min more before decomposition by rapid addition of a large excess of methanol. The usual work-up gave 0.32 g of crude product, which according to glpc analysis[57] contained >90% of a mixture of **9b** and **8b** (repetitive analyses gave variable ratios of these) and traces of **12** and a cleavage product (retention time relative to **9b** 0.30 at 260°). The nmr spectrum (CCl_4) had complex multiplets at τ 2.84, 4.25, and 7.25 in a ratio of 0.91:1.0:1.1; the ratio of aromatic to vinyl hydrogen here is in agreement with a composition of 97% of **8b** and 3% of **12**. The product was mixed with 0.16 g of 5% Pd on carbon and subjected to slow distillation in a sublimation apparatus at 0.05 mm and a bath temperature of 115° for 4 hr. The nmr spectrum of the distillate showed disappearance of all vinylic and allylic hydrogens and appearance of characteristic complex multiplets at τ 2.31 and 2.38 and at 2.86 and 2.91 in a ratio of 13:94, as expected for a mixture containing 89% of **9b** and 11% of **12**.

Reaction of 1,1,1-Triphenylethane with Cs–K–Na Alloy. A. Preparation of 9-Methyl-9-phenyl-2,4a,4b,7-tetrahydrofluorene (8c).—The alloy (2.00 ml, 38.8 mg-atoms) was vigorously stirred in the usual apparatus with 240 ml of THF at reflux for 1 hr. The solution was cooled to −70° (deep blue solution, doubtlessly containing some dissolved alkali metal) and a solution of 1,1,1-triphenylethane (0.61 g, 2.37 mmol) in 10 ml of THF was added dropwise with vigorous stirring over a period of 3 min. The solution readily acquired a red color and after 1 hr of stirring at −70° the deep brown-red solution was jetted into a 650-ml slush of ice and water. The mixture was concentrated to 200 ml on a rotating evaporator, chilled in an ice bath, and filtered to yield 240 mg of crystals, mp 94–96°. Analysis of these crystals by glpc[61] on a 6 ft × 1/8 in. column packed with 5% SE-30 on 100/120 mesh Aeropak-30 at 180° indicated that they consisted of about 97% of a compound identified as **8c** and 3% of a compound tentatively identified as 9-methyl-9(2,5-dihydrophenyl)-2,4a,4b,-7-tetrahydrofluorene. In another experiment extraction of the concentrated aqueous reaction mixture with ether gave a product which consisted of >90% of **8c** according to analsysis by glpc. Recrystallization from ethyl alcohol gave 165 mg of white crystals, mp 96.5–97.5°.

Anal. Calcd for $C_{20}H_{20}$: C, 92.26; H, 7.74. Found: C, 92.09, 91.93; H, 7.94, 7.87.

This compound exhibited the following properties: nmr (CS_2) at 60 MHz τ 2.85 (5.0 H, multiplet, C_6H_5–), 4.25 and 4.37 (6.1 H, complex multiplet, vinylic H), 7.25 (6.2 H, broad multiplet, allylic H), 8.67 (3.0 H, singlet, CH_3–); at 100 MHz vinylic H τ 4.26 and 4.37 (6.0 H), allylic H 7.09 (2.0 H) and 7.29 (4.2 H); λ_{max}^{EtOH} 247 nm (ϵ 130), 253 (180), 258 (230), 264 (180), 268 (140); ir (KBr pellet) 3010 (m), 2955 (w), 2940 (w), 2900 (w), 2860 (m), 2825 (m), 2795 (m), 1630 (w), 1595 (w), 1485 (m), 1440 (m), 1360 cm^{-1} (m); mass spectrum, molecular ion M^+ 260, fragments *m/e* 245 (M − CH_3), 182 (M − C_6H_5 − H), 181 (M − C_6H_5 − 2 H), 167 (M − C_6H_5 − CH_3 − H), 165 (M − C_6H_5 − CH_3 − 3 H).

B. Preparation of 9-Methyl-9-phenyl-2,4a,4b,7-tetrahydrofluorene-2,7-d_2.—1,1,1-Triphenylethane (600 mg, 2.32 mmol) was again allowed to react with 2.0 ml of Cs–K–Na alloy according to the previous procedure. This time the red solution was titrated at −70° with a 1.2 *M* solution of D_2O (98.7 atom % D) in THF until the color changed from red to blue-green (9.9 mmol of D_2O was consumed; evidently there was much direct reaction of alloy with D_2O). The reaction mixture was jetted into 650 ml of ice water and then concentrated to 200 ml on a rotating evaporator. The mixture was extracted with three 70-ml portions of ether and the ether extract was dried over anhydrous $MgSO_4$. The ethereal solution upon evaporation yielded a light yellow, crystalline residue which upon recrystallization from ethyl alcohol gave 430 mg (71% yield) of crystals, mp 96–97.5°. This compound gave nmr absorption in CS_2 at 60 MHz at τ 2.85 (5.0 H), 4.25 (6.2 H), 7.12 and 7.30 (4.5 H), 8.67 (3.0 H); at 100 MHz the vinylic protons were at τ 4.26 and 4.37 (6.0 H) and the allylic protons at 7.09 (1.9 H) and 7.35 (2.5 H).

C. Dehydrogenation of 9-Methyl-9-phenyl-2,4a,4b,7-tetrahydrofluorene.—A carbon disulfide solution of a 100-mg portion of the above 9-methyl-9-phenyl-2,4a,4b,7-tetrahydrofluorene-2,7-d_2 was intimately mixed with 100 mg of 5% palladium on carbon catalyst (from Englehard Industries), the solvent was removed *in vacuo*, and the mixture was heated for 2.5 hr at 100–120° under a nitrogen atmosphere. The product was then distilled from the catalyst at 0.1 mm with a bath temperature of 100°. This oily product, according to analysis by glpc, consisted of about 95% **9c** and 5% 1,1,1-triphenylethane. The oil was recrystallized from ethyl alcohol to give crystals of mp 79–81° which when mixed with an authentic sample of **9c** (mp 85–87°) melted at 80–83.5°. The infrared spectrum of this product was essentially identical with that of authentic **9c**.

Repetition of this dehydrogenation procedure with a protium sample of **8c** (mp 96.5–97.5°) but with a time of only 2 hr gave by glpc analysis a product which consisted of 68% **9c**, 6% 1,1,1-triphenylethane, and the remainder starting material. The presence of **9c** in one such dehydrogenation mixture was further confirmed by the uv spectrum of the mixture, which showed characteristic maxima at 265, 293, and 304 mμ as found for authentic **9c**.

As a test of the present dehydrogenation procedure a sample of 1,1,1-triphenylethane (0.30 g) in carbon disulfide was mixed with 0.30 g of the 5% palladium on carbon catalyst, the solvent was removed *in vacuo*, and the mixture was held at 100–110° under a nitrogen atmosphere for 3 hr. The product was separated by sublimation at 0.1 mm and was shown by glpc analysis to consist of only 1,1,1-triphenylethane. This hydrocarbon is, therefore, not dehydrogenated to **9c** under the present mild conditions.

D. Titration with *tert*-Butyl Alcohol.—1,1,1-Triphenylethane (600 mg, 2.32 mmol) was allowed to react with 2.0 ml of Cs–K–Na alloy in 200 ml of tetrahydrofuran at −70° for 1 hr according to the procedure given previously. The deep red solution, while being stirred at −70°, was then rapidly titrated with a 0.906 *M* solution of *tert*-butyl alcohol in tetrahydrofuran to an end point changing from red to blue-green. This required 4.98 ml (4.52 mmol) of *tert*-butyl alcohol (1.95 mol of alcohol per mol of 1,1,1-triphenylethane). In a repetition of this experiment 1.98 mol of *tert*-butyl alcohol was required per mol of 1,1,1-triphenylethane. The reaction mixture was immediately jetted into ice water. Analysis of the product by glpc showed the presence of about 91% **8c** and 9% of a material of slightly longer retention time believed to be 9-methyl-9(2,5-dihydrophenyl)-2,4a,4b,7-tetrahydrofluorene. Recrystallization from ethyl alcohol gave a product, mp 95–97°, whose composition (*via* glpc analysis) was, however, the same as before recrystallization.

Repetition of the experiment with 0.300 g (1.16 mmol) of 1,1,1-triphenylethane and 1.00 ml (19.4 mg-atoms) of Cs–K–Na alloy but with a slow addition of 1.77 g (24 mmol) of *tert*-butyl alcohol in 10 ml of tetrahydrofuran over a period of 45 min to the initial deep red solution, followed by jetting into ice water, gave a product which by glpc analysis consisted of about 67% of **8c** and 33% of 9-methyl-9(2,5-dihydrophenyl)-2,4a,4b,7-tetrahydrofluorene. The nmr spectrum in CS_2 showed aromatic (τ 2.8), vinylic (4.15 and 4.25–4.60), and allylic (7.2–7.4) hydrogen peaks in a ratio of 1.0:1.9:2.0. A 2:1 mixture of the above tetrahydrofluorene and hexahydrofluorene should give a theoretical ratio of 1.0:2.1:2.2 for these protons. Dehydrogenation of this product with 5% palladium on carbon at 100–110° for 3 hr gave a mixture which consisted of 45% of 1,1,1-triphenylethane and 55% of 9-methyl-9-phenylfluorene (glpc analysis). Evidently the hexahydrofluorene gives largely 1,1,1-triphenylethane under the present conditions of dehydrogenation.

Reaction of 2-Chloro-1,1,1-triphenylethane with Cs–K–Na Alloy.—In the usual apparatus was placed 2.0 ml (0.036 g-atom) of Cs–K–Na alloy and 200 ml of THF. The mixture was stirred at reflux for 1 hr and then cooled to −65°. A solution of 4.39 g (15.0 mmol) of 2-chloro-1,1,1-triphenylethane[31] in 25 ml of THF was added dropwise over a period of 30 min and stirring was continued for 7 min more at −65° before carbonation of the deep brown solution. Quantitative glpc analysis of the product gave 35% yield of 2,2,3-triphenylpropanoic acid, 2% yield of a mixture of some 10 volatile (as methyl esters) acids, some 4% of nonvolatile acids, 4.6% of 1,1,1-triphenylethane, 42% of un-

(61) At the flow rate used under these conditions the following retention times in minutes were observed: 1,1,1-triphenylethane, 7.2; 9-methyl-9-phenylfluorene, 8.5; 9-methyl-9-phenyl-2,4a,4b,7-tetrahydrofluorene, 9.6; and the compound tentatively identified as 9-methyl-9(2,5-dihydrophenyl)-2,4a,4b,7-tetrahydrofluorene, 10.8.

reacted 2-chloro-1,1,1-triphenylethane, and nonvolatile neutral products. During the course of work-up of the reaction products a crystalline material, mp 151.0–152.5° (from acetone), was isolated.

Anal. Calcd for 1:1 compound of $C_{20}H_{17}Cl$ and $C_{21}H_{18}O_2$: C, 82.74; H, 5.93; Cl, 5.96, average mol wt, 297.5 Found: C, 82.59; H, 6.14; Cl, 5.32; mol wt (acetone), 289.

The above analysis is in essential agreement with a 1:1 compound of 2-chloro-1,1,1-triphenylethane[31] (mp 101.0–101.8°) and 2,2,3-triphenylpropanoic acid[31] (mp 132.0–133.0°). This postulated composition was qualitatively confirmed[62] by glpc, nmr, uv, and mass spectral analyses.

Registry No.—**8c**, 33884-94-5; **9a**, 33884-95-6; **11**, 33884-96-7; 4-chloro-1,1,1-triphenylbutane, 33884-97-8; 5-chloro-1,1,1-triphenylpentane, 33884-98-9; 1,1,1-triphenylethane, 5271-39-6; lithium, 7439-93-2; potassium, 7440-09-7; cesium, 7440-46-2; sodium, 7440-23-5; 1,1,1-triphenylpentane, 13630-39-2; 2-chloro-1,1,1-triphenylethane, 33885-01-7; 5,5,5-triphenylpentanenitrile, 33885-02-8; 5,5,5-triphenylpentanoic acid, 33885-03-9; methyl 5,5,5-triphenylpentanoate, 33885-04-0; 2,2,5-triphenylpentanoic acid, 33885-05-1; 1,1,4-triphenylbutane, 33885-06-2; 6,6,6-triphenylhexanenitrile, 33885-07-3; 6,6,6-triphenylhexanoic acid, 33885-08-4; 1,1,5-triphenylpentanol-1, 33885-09-5; 9-methyl-9-phenyl-2,4a,4b,7-tetrahydrofluorene-*2,7-d*$_2$, 33885-10-8; 1:1 compound of 2-chloro-1,1,1-triphenylethane and 2,2,3-triphenylpropanoic acid, 33885-11-9.

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The Influence of Chelation on the Grignard Reactions of Some β-Hydroxy Ketones[1]

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β-Hydroxy ketones, having one of the oxygen-containing functions situated on a five- or six-membered carbon ring and the other on a side chain, undergo highly stereoselective Grignard reactions except when chelation is sterically inhibited. Thus, 2-α-hydroxyalkyl- (or 2-hydroxyaryl-) cyclopentanones and cyclohexanones yield pure diols. *cis*-2-Acylcyclopentanols also undergo stereospecific additions whereas similar reactions of *trans*-acylcyclopentanols resulted in poor yields and low stereoselectivity. By contrast, *trans*-2-acylcyclohexanols reacted stereospecifically and in high yields with Grignard reagents. The results are correlated with the readiness of reactants to form chelates.

The preferential formation of a major diastereomer in Grignard reactions of open-chain α-hydroxy ketones, in which the carbonyl group is adjacent to a chiral center, has been explained by the intermediacy of a chelate.[2] Similar reactions of β-hydroxy ketones were found to be less stereoselective and the results were explained by an "open-chain" instead of a "cyclic" transition state.[3]

Grignard reactions of β-hydroxy ketones in which one of the oxygen-containing functions is situated on a five- or six-membered carbon ring constitute the present study. The purpose of this investigation was to correlate the results of reactions (expressed in stereoselectivity and yields) with the stereochemical readiness of the organic substrates to form chelates with the metallic ion.

Results

Stereoisomeric *cis*- and *trans*-2-hydroxycyclopentanecarboxylic ethyl esters were used for the synthesis of several β-hydroxy ketones in the cyclopentane series. The chromatographic separation into cis (**1a**) and trans (**1b**) esters was achieved and therefore the previously used[4] procedure *via* separation of their 3,5-dinitrobenzoates was unnecessary. The difference between the chemical shifts of the methylene quartet of the ester function in the nmr spectrum proved to be a better criterion for the determination of isomeric purity than the previous assignment based on the band width of the proton adjacent to the hydroxyl group.[4b] Ketols **2** and **3** (Table I) were prepared from *cis*-hydroxy ester **1a** by the corresponding Grignard reactions followed by Jones oxidation. Six-membered homologs **7** and **8** were preferentially prepared from *trans*-2-hydroxycyclohexanecarboxylic esters by the same sequence. 2-Benzhydrylcyclopentanone **6** was obtained by dehydration of hydroxy ketone **2** to 2-benzylidenecyclopentanone and subsequent hydrogenation. *cis*- and *trans*-2-benzoyl- and -2-acetylcyclopentanols (**20a**, **20b**, **21a**, and **21b**, Table II) were prepared from *cis*-2-hydroxycyclopentanenitrile and MeMgBr or PhMgBr, respectively, followed by the hydrolysis of formed imines. Equilibration occurred during these reactions and the mixture of cis and trans ketols was separated by chromatography. Compounds **20a** and **20b** were also obtained from the reaction of *trans*-hydroxy ester **1b** with PhMgBr (see Experimental Section). Stereochemical assignments in this series were based on the differences in hydroxyl stretching frequencies in the infrared spectra: unlike *cis*-2-acylcyclopentanols, the trans isomers do not show the presence of intramolecular hydrogen bonding (Table III). Independent synthesis of diols **24a** and **27a** from *cis*-hydroxy ester **1a** served as an additional proof for the cis configuration of compounds **20a** and **21a**.

(1) A portion of this work has appeared in preliminary form: E. Ghera and S. Shoua, *Chem. Commun.*, 398 (1971).

(2) (a) D. J. Cram and K. R. Kopecky, *J. Amer. Chem. Soc.*, **81**, 2748 (1959); (b) D. J. Cram and D. R. Wilson, *ibid.*, **85**, 1245 (1963).

(3) T. J. Leitereg and D. J. Cram, *ibid.*, **90**, 4019 (1968).

(4) (a) J. Pascual and J. Castells, *ibid.*, **74**, 2899 (1952); (b) H. Baumann, N. C. Franklin, and H. Mohrle, *Tetrahedron*, **23**, 433 (1967).

TABLE I

GRIGNARD REACTIONS OF 2-SUBSTITUTED CYCLOALKANONES

Reactant	Reagent	Product[a]	Overall yield, %	Stereoselectivity, %
		$n = 1$		
2, $R_1 = R_2 = Ph$; $R_3 = OH$	MeMgBr	**11**, $R_4 = OH$; $R_5 = Me$	68	100
3, $R_1 = R_2 = Me$; $R_3 = OH$	PhMgBr	**12**, $R_4 = OH$; $R_5 = Ph$	60	100
4,[b] $R_1 = Ph$; $R_2 = H$; $R_3 = OH$	MeMgJ	**13**, $R_4 = OH$; $R_5 = Me$	71	100
5,[c] $R_1 = R_2 = H$; $R_3 = OH$	PhMgBr	**14**, $R_4 = OH$; $R_5 = Ph$	32[d]	100
6, $R_1 = R_2 = Ph$; $R_3 = H$	MeMgJ	**15a**, $R_4 = OH$; $R_5 = Me$	78[e]	56[e]
	MeMgBr	**15b**, $R_4 = Me$; $R_5 = OH$	81[f]	75[f]
		$n = 2$		
7, $R_1 = R_2 = Ph$; $R_3 = OH$	MeMgBr	**16**, $R_4 = OH$; $R_5 = Me$	38[g]	100
8,[h] $R_1 = R_2 = Me$; $R_3 = OH$	PhMgBr	**17**, $R_4 = OH$; $R_5 = Ph$	27[i]	100
9,[j] $R_1 = Ph$; $R_2 = H$; $R_3 = OH$	MeMgBr	**18**, $R_4 = OH$; $R_5 = Me$	78	100
10,[k] $R_1 = Me$; $R_2 = H$; $R_3 = OH$	PhMgBr	**19a**, **19b** $R_4 = OH$; $R_5 = Ph$	54	100

[a] Data on reaction conditions and newly prepared compounds are given in the Experimental Section and Table IV; the limit of detection for the minor diastereomer is <1%. [b] Pure diastereomer. [c] *Cf.* T. Takahashi, A. Kato, and S. Matsuoka, *Chem. Abstr.*, **54**, 4543*f* (1960). [d] α-Methylbenzyl alcohol and cleavage products were also formed. [e] For MeMgJ. [f] For MeMgBr; the values represent per cent of **15a** in the epimeric mixture. [g] Starting material and diphenylmethylcarbinol were also isolated. [h] J. Wolinsky, M. Senyek, and S. Cohen, *J. Org. Chem.*, **30**, 3207 (1965). [i] About 50% of starting material was recovered in variable reaction conditions. [j] *Cf.* ref 7. [k] *Cf.* F. Fries and F. Broich, *Chem. Abstr.*, **53**, P7056*g* (1959). Compound **10** consisted of a diastereomeric mixture inseparable by distillation or chromatography, as evidenced by nmr spectroscopy; both products, **19a** and **19b**, were cis diols (see Experimental Section).

TABLE II

GRIGNARD REACTIONS OF 2-ACYLCYCLOALKANOLS

Reactant	Reagent	Product[a]	Overall yield, %	Stereoselectivity, %[b]
		$n = 1$		
20a, R = Ph; R_1 = OH; R_2 = H	PhMgBr	**24a**, R_3 = Ph	72	
	MeMgBr	**25a**, R = Ph; R_3 = Me	76	93
		26a, R = Me; R_3 = Ph	6	
20b, R = Ph; R_1 = H; R_2 = OH	PhMgBr	**24b**, R_3 = Ph	7[c]	
	MeMgBr[d]	**25b**, R_3 = Me; R = Ph	16	60
		26b, R = Me; R_3 = Ph	11	
21a, R = Me; R_1 = OH; R_2 = H	PhMgBr	**26a**, R = Me; R_3 = Ph	73	100
	MeMgBr	**27a**, R_3 = Me	70	
21b, R = Me; R_1 = H; R_2 = OH	MeMgBr	**27b**, R_3 = Me	15	
		$n = 2$		
22a, R = Ph; R_1 = OH; R_2 = H	PhMgBr	**28a**,[e] R_3 = Ph	41	
	MeMgBr	**29a**, R = Ph; R_3 = Me	49	100
22b, R = Ph; R_1 = H; R_2 = OH	PhMgBr	**28b**,[e] R_3 = Ph	82	
	MeMgBr	**29b**, R = Ph; R_3 = Me	82	100
23, R = Me; R_1 = H; R_2 = OH	PhMgBr	**30b**, R = Me; R_3 = Ph	83	100
	MeMgBr	**31b**,[e] R_3 = Me	84	

[a] The substituents not mentioned in the product are the same as in the reactant. [b] Values are given for reactions in which a new chiral center is formed and represent per cent of the major isomer in the diastereomeric mixture. [c] All other products from this reaction were obtained in about the same yields and by the manner shown for the reaction of **1b** and PhMgBr (see Experimental Section). [d] The reaction mixture yielded, in order of chromatographic elution, 1-benzoylcyclopentene, **20b**, **26b**, and **25b**. [e] *Cf.* ref 21.

All Grignard reactions of hydroxy ketones were carried out with excess of reagent and the crude reaction mixtures were submitted to tlc and nmr analysis. Isomeric diols (if present) usually showed chemical-shift differences for the methyl proton signals and for the protons adjacent to the hydroxyl groups. All diols were separated from by-products by column chromatography.

Hydroxy ketones **2–5** (Table I) afforded pure diols to which the cis configuration was assigned on the basis of presence of intramolecular hydrogen bonding in the infrared spectra. Trans diols (*e.g.*, **25b** or **26b**, Table III) were devoid of intramolecularly bonded OH.[5]

In the cyclohexane series, similar reactions of hydroxy ketones **7–10** also resulted in the formation of cis diols exclusively. The assignment of configuration was based on the known preference for trans attack in 2-

(5) The relative large torsional angles for vicinal trans substituents in cyclopentanes are responsible for this difference; see E. L. Eliel, N. A. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965, p 203.

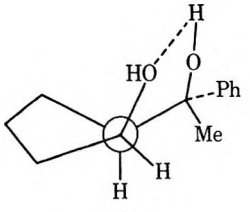
TABLE III
INFRARED HYDROXYL STRETCHING FREQUENCIES[a]

Compound	ν_{free}[b]	ν_{bonded}
3	3623 (sh)	3529 (s)
8	3633 (sh)	3548 (s)
12	3637 (w)	3509 (s)
20a	3646 (sh)	3509 (s)
20b	3629	
21a		3537 (br)
21b	3630	
25a	3673 (w)	3506
26a	3634 (w)	3526
25b	3630	
26b	3611	
27a	3635 (w)	3507 (s)

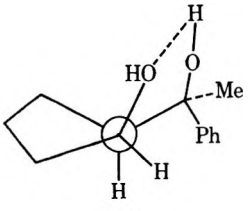
[a] Recorded on a Beckman IR-7 spectrophotometer. The concentration was 0.02 *M* in Spectrograde CCl_4. [b] s, strong; sh, shoulder; w, weak; br, broad.

substituted cyclohexanones[6] and previous observations.[7] In variance with compounds **2** and **3**, their six-membered homologs **7** and **8** reacted in lower yields and significant amounts of starting material were recovered. The reactions of 2-benzhydrylcyclopentanone (**6**, devoid of a chelating hydroxyl group) with MeMgI and MeMgBr were less stereoselective and the configurational assignments of the obtained isomeric alcohols **15a** and **15b** were based on nmr evidence (the methine proton was deshielded when cis oriented to the hydroxyl group).

Grignard reactions of *cis*-acylopentanols (Table II) were characterized by good yields and high stereoselectivity. Thus, *cis*-2-benzoylcyclopentanol (**20a**) afforded, with MeMgBr, the diol **25a** (93% stereoselectivity), whereas *cis*-2-acetylcyclopentanol and PhMgBr yielded its diastereomer (**26a**) exclusively. The nmr spectra were in agreement with the shown configurations in which the stablest conformation implies intramolecular hydrogen bonding and pseudoequatorial orientation for the side chain.



25a

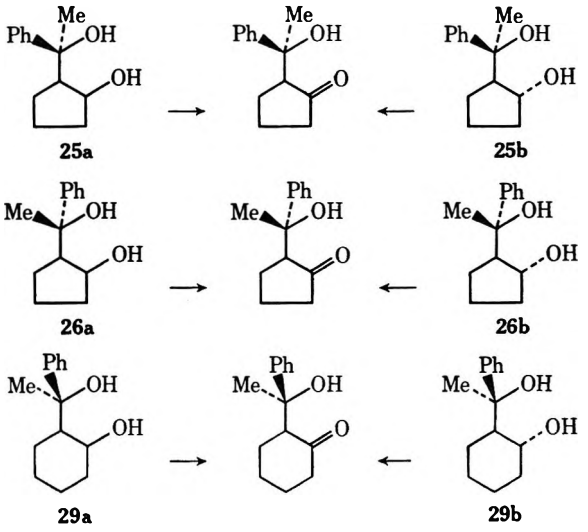


26a

In **26a** the proton adjacent to the hydroxyl group is shielded (δ 3.77) owing to the anisotropy of the phenyl group (above or below the plane of the aromatic ring), whereas in **25a** it is not (δ 4.64). Conversely, the methyl group is relatively nearer to the secondary hydroxyl group in **25a** (δ 1.70) than in **26a** (δ 1.38).

The corresponding *trans*-2-acylcyclopentanols behaved very differently in terms of yields of diols and stereoselectivity of reactions. Unlike the cis isomer, *trans*-2-benzoylcyclopentanol (**20b**) afforded with MeMgBr only small amounts of diastereomeric diols **25b** and **26b** and some of the starting material was recovered. The stereochemical assignments for trans diols **25b** and **26b** were based on oxidation results and correlation with cis diols (Scheme I).

SCHEME I



The particular reaction of **20b** and PhMgBr afforded (in order of chromatographic elution) 1-benzoylcyclopentene (24%), cis ketol **20a** (13%), trans diol **24b** (8%), and trans ketol **20b** (28%). α-Methylbenzyl alcohol was also obtained (in amounts varying between 5 and 20% of the total material) even when the reaction was conducted under pure nitrogen.[8] The latter compound was not detected in an identical reaction of **20a** and its formation might be due to lower reactivity of **20b** toward PhMgBr.[9]

In reactions paralleling those of 2-acylcyclopentanols, *cis*-hydroxy ester **1a** afforded readily the corresponding diols whereas trans isomer **1b** gave results similar to those obtained from trans ketols **20b** and **21b**. Hence the conversion, *trans*-hydroxy ester → trans ketol takes place normally.

In contrast to *trans*-2-acylcyclopentanols, Grignard reactions of *trans*-2-acylcyclohexanols proceeded with complete stereospecificity and very good yields; the pure diol (**29b**) obtained from **22b** and MeMgBr was diastereomeric with diol **30b**, formed exclusively in the reaction of **23b** and PhMgBr. The configurational assignment for **29b** was based on the chemical shift of the proton adjacent to the hydroxyl group which showed strong shielding (δ 3.11) owing to the anisotropy of the phenyl group in a hydrogen-bonded conformation. In the cis series, 2-benzoylcyclohexanol **22a** afforded comparatively lower yields of diols. Jones oxidation of the diol **29a** and correlation with the diol **29b** (Scheme I) provided the configurational assignment.

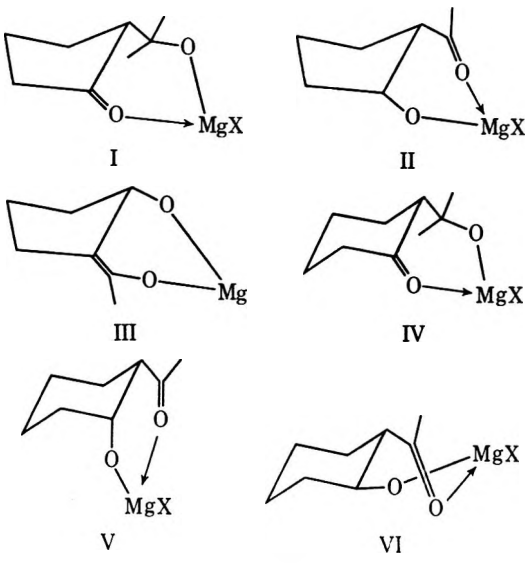
In agreement with the above results, Grignard reactions of *trans*-2-hydroxycyclohexanecarboxylic esters also afforded significantly higher yields of diols than the corresponding *cis*-hydroxy esters (see Experimental Section).

(6) G. Di Maio, M. T. Pellegrini, and P. A. Tardella, *Ric. Sci.*, 240 (1968); *Chem. Abstr.*, **69**, 77064f (1968).

(7) H. E. Zimmermann and J. English, *J. Amer. Chem. Soc.*, **76**, 2285 (1954).

(8) The formation of this compound was reported to occur when ether solutions of PhMgBr were exposed to oxygen [*e.g.*, C. Walling and S. A. Buckler, *ibid.*, **77**, 6032 (1955)].

(9) Free radicals were detected in THF solutions of phenyl ketones in presence of PhMgBr and their concentration depended on the concentration of reagents. *Cf.* K. Maruyama, *Bull. Chem. Soc. Jap.*, **37**, 897 (1964).



Discussion

The accepted "reactant-like" transition state for Grignard additions[10] and the stereochemical assignments for the products obtained permit the discussion of results in terms of cyclic models I–VI. In these models a distorted half-chair conformation can probably be assumed for the chelated rings on the basis of tetrahedral orientation of Mg bonds, greater O–Mg bond distances (2.10 Å) and recent conformational studies on 1,3 heterocycles.[11] Inspection of steric models shows that there is a relationship between the conformational and configurational properties of reactants and the stereoselectivity and yields of additions: an orientation of C–O bonds which allows formation of chelates with lesser strain and lesser nonbonded interactions ensures higher yields and stereospecificity in Grignard reactions. Thus, the addition to models I and IV is stereospecific because the "endo" approach (from below) of the reagent is hindered. By contrast, in nonchelated 2-substituted cyclopentanones[12] and cyclohexanones[6] the minor stereoisomeric Grignard adduct was usually also formed. Even the presence of a bulky substituent (in compound **6**) did not prevent the formation of the minor isomer. Recovery of starting material from reactions of compounds **7** and **8** suggests that nonbonded interactions between bulky substituents and ring bonds are stronger in chelates formed from cyclohexane than cyclopentane derivatives[13] and therefore tautomeric shifts enable the formation of less hindered chelates by enol participation.

The Grignard reactions of stereoisomeric 2-acylcyclopentanols permitted to establish the difference in behavior between the isomers able to form chelates and those unable to do so. Model II allowed a stereoselective approach of the reagent (from above) and the addition yields were probably enhanced by bond polarization. By contrast, addition of reagents to *trans*-2-acylcyclopentanols was inhibited and not stereoselective. Isolation of both **20a** and **20b** from the reaction of *trans*-2-benzoylcyclopentanol (**20b**) with PhMgBr and the loss of deuterium in the above compounds (when deuterated **20b** in the α position to the carbonyl was used in this reaction) show that the ketone–enol equilibrium was shifted toward the enol and the chelate (model III) was formed by the flattening of the molecule. 1-Benzoylcyclopentene, which was also obtained in the above reaction, was not formed under similar conditions from the cis isomer **20a** where a trans elimination would favor its formation. Hence the elimination occurred from complex III.

Participation of two (trans) equatorial bonds in the formation of a nonstrained chelate VI ensured stereospecific high-yield addition to *trans*-acylcyclohexanols by the approach of the reagent from the less hindered side (from above). In *cis*-acylcyclohexanols chelate formation involves an axial and an equatorial bond (model V) and the lesser stability of a pseudo cis-fused bicyclic model is reflected mainly in lower yields of diols.

In conclusion, the results obtained indicate the possibility of asymmetric synthesis starting from a variety of acylcycloalkanols.[14]

In open-chain β-hydroxy ketones the cyclic models did not predict the correct addition results and it has been assumed that this may be due to the possible lower stability of six- than five-membered chelated rings.[3] Present results show however that six-membered chelates of β-hydroxy ketones can be readily formed. Hydride reductions of some open-chain β-hydroxy ketones, monosubstituted at the central carbon atom, were reported[15,16] to be stereoselective owing to attack from the less hindered side of a cyclic model, in respect to the α substituent. It seems therefore reasonable to assume that a cyclic model also predominates in the transition state of the reported[3] Grignard reactions of 4-hydroxy-4-phenyl-2-pentanone and 1,3-diphenyl-3-hydroxy-1-butanone, but that the effect bulks of the β substituents, in absence of an α substituent to the carbonyl group, do not exercise an orienting effect.[17] Substitution at the central carbon atom in the presently studied β-hydroxy ketones exercised a decisive orienting effect, when chelation was sterically possible.

Experimental Section

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. Nmr spectra were obtained on a Varian A-60 spectrometer using tetramethylsilane as an internal standard and $CDCl_3$ as solvent. Florisil 60–100 mesh was used for column chromatography, if not specified otherwise. Silica gel Merck (0.05–0.2 mm) was used in columns loaded by the "dry column" method[18] (the components were eluted by the standard manner).

Separation of *cis*- and *trans*-2-Hydroxycyclopentanecarboxylic

(10) *Cf.* (a) G. J. Karabatsos, *J. Amer. Chem. Soc.*, **89**, 1367 (1967); (b) M. Cherest and H. Felkin, *Tetrahedron Lett.*, 2205 (1968).

(11) E. L. Eliel, *Accounts Chem. Res.*, **3**, 1 (1970).

(12) J. P. Battioni, M. L. Capmau, and W. Chodkiewicz, *Bull. Soc. Chim. Fr.*, 976 (1969).

(13) The intramolecular hydrogen bonding is somewhat stronger in compound **3** (i.e., $\Delta\nu$ is greater) than in compound **8** (Table III).

(14) A stereospecific Grignard addition to 1-acyl-2-methoxycyclohexane, part of a thebaine derivative, was reported by K. W. Bentley, D. G. Hardy, and B. Meek, *J. Amer. Chem. Soc.*, **89**, 3273 (1967). In this particular case the approach to one of the carbonyl faces was hindered by the presence of an etheno bridge in the cyclohexane ring.

(15) J. P. Maffrand and P. Maroni, *Bull. Soc. Chim. Fr.*, 1408 (1970).

(16) S. Yamada and K. Koga, *Tetrahedron Lett.*, 1711 (1967).

(17) The assumption of the authors that the stereoselectivity is predicted by an open-chain model was mainly based on results obtained in the reaction of 4-hydroxy-4-phenyl-2-pentanone and PhMgBr. Repeating the determination of the OH stretching frequency in the infrared spectrum of the above hydroxy ketone (in 0.02 *M* CCl_4 solution), we found only a broad absorption between 3480 and 3520 cm^{-1} which is in complete agreement with a chelated (by hydrogen bonding) rotamer.

(18) B. Loev and M. M. Goodman, *Chem. Ind. (London)*, 2026 (1967).

Ethyl Esters 1a and 1b.—The mixture of stereoisomers[4a] (10 g) was separated by chromatography using the "dry column" method. Elution with pentane and 20% ether afforded first the cis isomer **1a** (6.4 g), nmr δ 4.20 (q, 2, $COOCH_2$–, J = 7 Hz), followed by a few fractions of a mixture of **1a** and **1b** and then pure trans isomer **1b** (2.6 g), nmr δ 4.16 (q, 2, $COOCH_2$–, J = 7 Hz).

In an alternative preparation of *trans*-hydroxy ester **1b**, a mixture of *trans*-2-hydroxycyclopentanecarbonitrile[19] (18 g) and 150 ml of 15% aqueous KOH was refluxed during 4 hr, cooled, washed with ether, acidified with 10% HCl, and extracted with ether. The ether solution was dried and evaporated *in vacuo*, and the residue was dissolved in absolute ethanol (150 ml) saturated with hydrogen chloride. After 5-hr reflux the solvent was distilled *in vacuo* and water was added and the mixture was extracted with ether. The residue left after evaporation of the solvent was chromatographed as shown above to give 8.2 g of **1b**.

Grignard Reactions of Hydroxy Esters 1a and 1b. General Procedure.—A solution of the hydroxy ester (10 mmol) in 100 ml of dry ether was added dropwise under nitrogen to the ice-cooled solution of the Grignard reagent (PhMgBr or MeMgJ, 80 mmol in 100 ml of dry ether). The mixture was stirred (4 hr for PhMgBr and overnight for MeMgJ) at room temperature, then hydrolized with excess of NH_4C solution, the organic layer was separated, and the aqueous phase was extracted several times with ether. The combined ether layers were washed (aqueous NaCl solution) and dried (Na_2SO_4), the solvent was evaporated *in vacuo*, and the residue was chromatographed.

The *cis*-hydroxy ester **1a** afforded by the above procedure the diols **24a**[20] (71% yield, elution with hexane and 10% ether) and **27a** (73% yield, elution with pentane and 20% ether), respectively.

In the reaction of hydroxy ester **1b** and MeMgJ about 70% of the material was not recovered by extraction. Chromatography of the residue gave a low yield (11%) of diol **27b** (elution with pentane and 30% ether).

The residue (2 g) from the reaction of **1b** and PhMgBr was chromatographed on silica by the dry column method and afforded 0.52 g of 1-benzoylcyclopentene (23% yield, elution with pentane and 5% ether), varying amounts of α-methylbenzyl alcohol (0.1–0.4 g, pentane and 10% ether), *cis*-2-benzoylcyclopentanol (**20a**, 0.35 g, 14% yield, elution with pentane and 30% ether), *trans*-2-(α-hydroxybenzhydryl)cyclopentanol (**24b**, 0.16 g, 5% yield), and *trans*-2-benzoylcyclopentanol (**20b**, 0.64 g, 26% yield, pentane and 40% ether). The separation of **24b** and **20b** was completed by repeated chromatography, using as eluents 20% benzene and 80% methylene chloride. 1-Benzoylcyclopentene had bp 92° (0.5 mm), n^{25}D 1.564, nmr δ 6.53 (m, 1, $w_{1/2}$ = 5 Hz), uv max (EtOH) 251 nm (ϵ 16100), ir ($CHCl_3$) 1680 cm^{-1}.

Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.52; H, 7.21.

The previously reported reactions[21] of *cis*- and *trans*-2-hydroxycyclohexanecarboxylic esters with PhMgBr and MeMgI were repeated (in conditions shown for **1a** and **1b**) to determine and compare the yields of diols obtained from both stereoisomers. *cis*-2-(α-Hydroxybenzyhydryl)cyclohexanol (**28a**) and *cis*-2-(α-hydroxyisopropyl)cyclohexanol were obtained in 42 and 64% yields, respectively (after chromatographic purification), whereas the corresponding trans isomers (**28b** and **31b**) were formed in 82 and 84% yields.

Preparation of Hydroxy Ketones 2, 3, and 7 (Table I).—The diol (10 mmol) was dissolved in acetone (25 ml for diols **27a** and **31b**) and 75 ml for **24a**) and 2.5 ml of Jones reagent was added dropwise to the cooled solution (5°). After stirring for 5 min the mixture was diluted with water and extracted with chloroform. The organic layer was washed (CO_3HNa and NaCl solutions), dried, and evaporated *in vacuo*.

Diol **24a** (2.68 g) afforded 1.70 g (64%) of 2-(α-hydroxybenzhydryl)cyclopentanone (**2**), mp 165° (from chloroform and hexane).

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.42; H, 6.78.

Diol **27a** (1.44 g) afforded, after chromatographic purification, 0.87 g (61%) of 2-(α-hydroxyisopropyl)cyclopentanone (**3**): bp 50–52° (0.3 mm); n^{20}D 1.458; nmr δ 1.19 (s, 3, CH_3), 1.41 (s, 3, CH_3).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.52; H, 10.12.

Diol **28b** (2.8 g) yielded 2.1 g (75%) of 2-(α-hydroxybenzydryl)-cyclohexanone (**7**), mp 174° (from chloroform and hexane).

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.18. Found: C, 81.25; H, 7.05.

2-(α-Hydroxybenzyl)cyclopentanone (4) was prepared by the method reported[22] for the six-membered-ring homolog. The unreacted cyclohexanone and benzaldehyde were eliminated by distillation *in vacuo* and the part of the residue which was soluble in ether was chromatographed by the dry column method. Compound **4** was obtained by elution with pentane and 5% ether, in 16% yield, mp 60–61°, (from hexane), nmr δ 5.25 (d, 1, CHOH, J = 3 Hz), ir ($CHCl_3$) 1735 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: 75.92; H, 7.48.

The diastereomer of **4** (δ 4.72, **d**, 1) was also present in the reaction mixture but was not isolated pure.

2-Benzhydrylcyclopentanone (6).—A solution of hydroxy ketone **2** (0.78 g) in 50 ml of benzene and 100 mg of *p*-toluenesulfonic acid were refluxed for 1 hr. The resulting yellow solution was washed (aqueous CO_3HNa solution and water), dried, and evaporated *in vacuo*. 2-Benzylhydrylidenecyclopentanone had mp 116–117° (from hexane).

Anal. Calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.50. Found: C, 87.31; H, 6.61.

The above compound (0.6 g) in 20 ml of methanol was hydrogenated over palladium on carbon powder. After absorption of the calculated volume of gas, the catalyst was removed by filtration and the solvent was evaporated. Chromatography of the residue (elution with pentane and 5% ether) afforded 0.42 g of **6**, mp 91–92° (from ether and pentane), nmr δ 4.64 (d, 1, Ph_2CH–, J = 5 Hz), ir ($CHCl_3$) 1736 cm^{-1}.

Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.12; H, 7.31.

***cis*- and *trans*-2-Benzoylcyclopentanols (20a and 20b).**—The reported[19] 2-hydroxycyclopentanenenitrile consisted of a stereoisomeric mixture which was separated by chromatography into trans isomer (72% of the total, elution with 1:1 pentane–ether) and cis isomer (28%, 1:2 pentane–ether). The trans configuration of the main isomer was verified as follows. A solution of the compound (0.5 g) in 10 ml of ethanol saturated with hydrogen chloride was kept at 10° for 48 hr. Evaporation of the solvent *in vacuo*, warming of the residue with 10 ml of water on a water bath during 30 min, and extraction with ether afforded the *trans*-hydroxy ester **1b** (0.32 g). The *cis*-hydroxy nitrile did not react in the above conditions.

To an ice-cooled solution of PhMgBr (from 10 g of PhBr) in 70 ml of dry ether was added a solution of 2-*cis*-hydroxycyclopentanenitrile[23] (1 g) in 25 ml of benzene and the reaction was continued at room temperature for 3 hr. Hydrolysis and extraction (as shown for Grignard reactions of esters) yielded a residue which was stirred for 45 min at room temperature with a mixture of 10% AcOH (10 ml) and 10% HCl (10 ml). Water was then added and the mixture was extracted twice with ether. The combined ether layers were washed with aqueous solutions of Na_2CO_3 and NaCl, dried, and evaporated to give a residue which was chromatographed on a silica "dry" column affording at first *cis*-2-benzoylcyclopentanol (**20a**, 130 mg, elution with pentane and 30% ether): bp 102° (0.15 mm); n^{21}D 1.556; nmr δ 3.60 (m, 1, COCH–), 4.62 (br, 1, CHOH, $w_{1/2}$ = 6 Hz); ir ($CHCl_3$) 1671 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.62; H, 7.38.

***trans*-2-Benzoylcyclopentanol (20b,** 255 mg) was eluted next with pentane and 40% ether: nmr δ 3.70 (m, 1, COCH–), 4.56 (br, 1, CHOH, $w_{1/2}$ = 8 Hz); ir ($CHCl_3$) 1676 cm^{-1}. The oil decomposed when distilled under reduced pressure and was characterized as the *p*-nitrobenzoate, mp 107° (crystallized from pentane and ether).

Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.42; H, 5.12, N, 3.92.

***cis*- and *trans*-2-Acetylcyclopentanols (21a and 21b).**—The *cis*-hydroxy nitrile (3 g) was treated with MeMgBr in conditions

(19) M. Mousseron, J. Julien, and F. Winternitz, *Bull. Soc. Chim. Fr.*, 878 (1948).

(20) All diols were obtained also from the corresponding hydroxy ketones (Table II). Data for new compounds are given in Table IV.

(21) H. E. Zimmerman and J. E. English, *J. Amer. Chem. Soc.*, **75**, 2367 (1953).

(22) D. Vorländer and K. Kunze, *Ber.*, **59**, 2079 (1926).

(23) The use of an isomeric mixture of 2-hydroxy nitriles lowered the reaction yields of this reaction.

TABLE IV

DATA ON THE PRODUCTS OF GRIGNARD REACTIONS

Compd[a]	Mp or bp (mm), °C	Nmr, δ (ppm)	Compd[a]	Mp or bp (mm), °C	Nmr, δ (ppm)
11	116–117[b]	0.95 (s, 3, CH_3)	24a	112–114[c]	4.29 (br, 1, CHOH, $w_{1/2}$ = 8 Hz)
12	105–106[c]	0.81 (s, 3, CH_3), 1.15 (s, 3, CH_3)	24b	119–120[c]	4.23 (br, 1, CHOH, $w_{1/2}$ = 10 Hz)
13	100–101[b,d]	1.41 (s, 3, CH_3), 5.15 (s, 1, PhCH, $w_{1/2}$ = 3Hz)	25a	79–80[e]	1.70 (s, 3, CH_3), 4.64 (br, 1, CHOH, $w_{1/2}$ = 6 Hz)
14	79–80[b]	3.64 (br, 2, CH_2OH)	25b	102–104[c,d]	1.59 (s, 3, CH_3), 3.97 (br, 1, CHOH, $w_{1/2}$ = 9 Hz)
15a	148–150 (0.25), $n^{20}D$ 1.566	0.77 (s, 3, CH_3), 4.04 (d, 1, PhCH, J = 11 Hz)	26a	130–132 (0.5), $n^{20}D$ 1.534	1.38 (s, 3, CH_3), 3.77 (br, 1, CHOH $w_{1/2}$ = 6 Hz)
15b	96–97[b]	1.20 (s, 3, CH_3), 3.72 (d, 1, PhCH, J = 12 Hz)	26b	80–81[b]	1.56 (s, 3, CH_3), 4.15 (br, 1, CHOH, $w_{1/2}$ = 9 Hz)
16	128–129[b]	0.74 (s, 3, CH_3)	27a	44–45[e]	1.19 (s, 3, CH_3), 1.40 (s, 3, CH_3), 4.47 (br, 1, CHOH, $w_{1/2}$ = 6 Hz)
17	115–116[b]	0.65 (s, 3, CH_3), 1.13 (s, 3, CH_3)	27b	83[b,d]	1.17 (s, 3, CH_3), 1.21 (s, 3, CH_3), 4.14 (br, 1, CHOH, $w_{1/2}$ = 9 Hz)
18	117[b]	1.47 (s, 3, CH_3), 5.43 (s, 1, PhCH, $w_{1/2}$ = 3 Hz)	29a	166–168[f]	1.67 (s, 3, CH_3), 4.62 (br, 1, CHOH, $w_{1/2}$ = 6 Hz)
19a	97[b]	0.99 (d, 3, CH_3, J = 7 Hz)	29b	128[e]	1.57 (s, 3, CH_3), 3.11 (br, 1, CHOH, $w_{1/2}$ = 13 Hz)
19b	130–132 (0.1), $n^{24}D$ 1.545	0.78 (d, 3, CH_3, J = 7 Hz)	30b	108–109[c]	1.61 (s, 3, CH_3), 3.72 (br, 1, CHOH, $w_{1/2}$ = 14 Hz)

[a] Satisfactory analytical data (±0.3%) were obtained for all compounds reported in the table: Ed. [b] Crystallized from pentane and ether. [c] Crystallized from hexane and chloroform. [d] Because of distillation difficulties the oily diol was characterized (melting point and elementary analysis) as the secondary mono-*p*-nitrobenzoate. [e] Crystallized from cold pentane. [f] Crystallized from ethanol.

shown for the preparation of **20a** and **20b**. The reaction mixture was hydrolyzed with a saturated solution of NH_4Cl and stirred with it for 2 hr at room temperature. The organic layer was separated and the aqueous layer was extracted with ether. Work-up and chromatography as shown previously yielded at first **21a** (0.22 g, elution with pentane and 30% ether): bp 85–88° (1.5 mm); $n^{18}D$ 1.468; nmr δ 2.23 (s, 3, CH_3), 4.52 (br, 1, CHOH, $w_{1/2}$ = 7 Hz); ir ($CHCl_3$) 1706 cm^{-1}.

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.76; H, 9.40.

After a few fractions containing a mixture of **21a** and **21b** (0.28 g), the pure trans isomer **21b** (0.52 g) was obtained: bp 86–88° (1.5 mm); $n^{19}D$ 1.465; nmr δ 2.22 (s, 3, CH_3), 4.40 (br, 1, CHOH, $w_{1/2}$ = 13 Hz); ir ($CHCl_3$) 1710 cm^{-1}.

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.72; H, 9.32.

Preparation of 2-Acylcyclohexanols (22a, 22b, and 23).—The reported[19] *trans*-2-hydroxycyclohexanecarbonitrile was found to consist of 90% trans isomer and 10% cis isomer. The isomers were separated as shown for the hydroxy nitriles in the cyclopentane series. The trans isomer (5 g) was treated with MeMgBr by the procedure used for the preparation of **21a** and **21b**. The product was purified by chromatography on silica (elution with pentane and 30% ether) to yield 3.2 g of *trans*-2-acetylcyclohexanol (**23**): bp 73–75° (0.8 mm); $n^{24}D$ 1.472; nmr δ 2.22 (s, 3, CH_3), 3.83 (br, 1, CHOH, $w_{1/2}$ = 14 Hz); ir ($CHCl_3$) 1700 cm^{-1}.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: 67.73; H, 10.02.

The reaction of *trans*-hydroxycyclohexanecarbonitrile (5.8 g) with an excess of PhMgBr was carried out under conditions given for **20a** and **20b** and afforded *trans*-2-benzoylcyclohexanol (**22b**, 2.8 g): mp 81–82° (from chloroform and hexane); nmr δ 3.38 (br, 1, COCH), 4.03 (m, 1, CHOH, $w_{1/2}$ = 21 Hz); ir ($CHCl_3$) 1672 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.28; H, 7.82.

The reaction of *cis*-2-hydroxycyclohexanenitrile (1 g) with PhMgBr was carried out under the same conditions except that longer exposure to acid (2 hr) was needed for the hydrolysis of the imine. *cis*-Benzoylcyclohexanol (**22a**, 0.46 g) had mp 72–73° (from ether and pentane); nmr δ 3.37 (m, 1, COCH), 4.27 (m, 1, CHOH, $w_{1/2}$ = 8 Hz); ir ($CHCl_3$) 1676 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: 76.18; H, 7.96.

Grignard Reactions of Compounds 2–10 and 20–23. General Procedure.—A solution of 10 mmol of ketone in 100 ml of dry ether (except the less soluble ketones **2** and **7**, which were dissolved in 200 ml of benzene) was added dropwise under nitrogen to an ice-cooled solution of 60 mmol of Grignard reagent in 100 ml of ether. Ketones **20a** and **22b** were preferably added at 18°. The reaction mixtures were stirred at room temperature for 4 hr (except compound **2** which was allowed to react overnight), decomposed by an excess of saturated NH_4Cl solution, and extracted with ether in the manner shown for Grignard reactions of hydroxy esters. The crude reaction mixtures were analyzed by tlc, ir, and nmr spectroscopy and then chromatographed on silica (dry column method) using pentane and ether as eluent mixture. The identical diol fractions (tlc) were combined and other fractions were also submitted to tlc and nmr analysis to determine if an isomeric diol was present. Data on newly prepared diols are given in Table IV.

The reaction of hydroxy ketone **10** (1 g, isomeric mixture) with PhMgBr in the above conditions yielded a mixture of diols which was partly separated by chromatography on silica (elution with pentane and 20% ether): diol **19a** (65 mg) was followed by several fractions containing both isomers (327 mg) and by the pure diol **19b** (480 mg). Both diols were separately submitted to Jones oxidation by addition of the reagent (0.1 ml) to the diol (60 mg) in acetone solution (3 ml) at 10°, under nitrogen. Addition of water (after 3-min stirring) and extraction with ether afforded in both cases, after chromatography (elution with pentane and 15% ether), 1-phenyl-*c*-2-acetyl-*r*-1-cyclopentanol (35 mg): mp 67° (from cold pentane); nmr δ 1.88 (s, 3, CH_3), 3.14 (t, 1, COCH); ir ($CHCl_3$) 1700 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 77.03; H, 8.31. Found: C, 76.83; H, 8.26.

The reactions of compound **20b** with MeMgBr yielded, in addition to diols **25b** and **26b**, also some 1-benzoylcyclopentene and starting material. The reaction of **20b** with PhMgBr gave results very similar to those obtained in the reaction of the *trans*-hydroxy ester **1b** and PhMgBr.

Jones oxidation of Diols 25a, 25b, 26a and 26b.—The corresponding diol (200 mg) was dissolved in 5 ml of pure acetone and treated with Jones reagent (0.25 ml) as described previously. Work-up and chromatographic purification (elution with 20–30% ether and pentane) afforded 110–120 mg (about 60% yield) of the hydroxy ketone. Some starting material was recovered from the column after the product was eluted. Diols **25a** and **25b** afforded by the above oxidation the same hydroxy ketone (2*RR*,2α*SS*)-2-(α-hydroxy-α-methyl)benzylcyclopentanone, mp 70–71° (from pentane and ether), nmr δ 1.72 (s, 3, CH_3), ir ($CHCl_3$) 1726 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.29; H, 7.82.

Diols **26a** and **26b** afforded (2*RS*,2α*SR*)-2-(α-hydroxy-α-methyl)benzylcyclopentanone, bp 85–87° (0.25 mm), $n^{20}D$ 1.535, nmr δ 1.58 (s, 3, CH_3), ir ($CHCl_3$) 1724 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.42; H, 7.78.

Separate oxidations of diols **29a** and **29b** by the same manner provided (2*RR*,2α*SS*)-2-(α-hydroxy-α-methyl)benzylcyclohexanone, bp 88–90° (0.4 mm), $n^{25}D$ 1.524; nmr δ 1.64 (s, 3, CH_3), ir ($CHCl_3$) 1698 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.85; H, 8.36.

Deuteration of *trans*-2-Benzoylcyclopentanol (20b).—A solution of **20b** (0.6 g) in dimethoxyethane (10 ml), D_2O (3 ml), and 40 mg of anhydrous Na_2CO_3 were refluxed for 16 hr. Extraction with ether and chromatography of the residue on a dry column afforded 0.32 g of 2-d_1-*trans*-2-benzoylcyclopentanol which was eluted with 40% ether and pentane. Nmr showed no chemical shift in the δ 3.5–4.0 region, mol wt 191 (mass spectrum).

Grignard reaction of deuteriated **20b** (0.3 g) with PhMgBr by the usual procedure yielded, along with other products, **20a** (30 mg) and **20b** (65 mg) which were separated by dry column chromatography as shown for the reaction of **1b** and PhMgBr. The exchange of deuterium on hydrogen was proven by nmr analysis and by mass spectral determination of molecular weight of **20a** and **20b** (190).

Registry No.—**2**, 32338-46-8; **3**, 32338-48-0; **4**, 32338-47-9; **6**, 30614-37-0; **7**, 33831-21-9; **11**, 33831-22-0; **12**, 33831-23-1; **13** *p*-nitrobenzoate, 33847-00-6; **14**, 33831-24-2; **15a**, 33831-25-3; **15b**, 33831-26-4; **16**, 33831-27-5; **17**, 33831-28-6; **18**, 33831-29-7; **19a**, 33872-39-8; **19b**, 33831-30-0; **20a**, 32346-66-0; **20b** *p*-nitrobenzoate, 33831-32-2; **21a**, 32435-36-2; **21b**, 33830-23-8; **22a**, 33830-24-9; **22b**, 33830-25-0; *trans*-**23**, 33830-26-1; **24a**, 33830-27-2; **24b**, 33830-28-3; **25a**, 33830-29-4; **25b** *p*-nitrobenzoate, 33847-01-7; **26a**, 33830-30-7; **26b**, 33830-31-8; **27a**, 33830-32-9; **27b** *p*-nitrobenzoate, 33847-02-8; **29a**, 33872-40-1; **29b**, 33830-33-0; **30b**, 33830-34-1; 1-benzocyclopentene, 21573-70-6; 2-benzylhydrylidenecyclopentanone, 14636-29-4; 1-phenyl-*c*-2-acetyl-*r*-1-cyclopentanol, 33830-37-4; (2*RR*,2α*SS*)-2-(α-hydroxy-α-methyl)benzylcyclopentanone, 33830-38-5; (2*RS*,2α*SR*)-2-(α-hydroxy-α-methyl)benzylcyclopentanone, 33830-39-6; (2*RR*,2α*SS*)-2-(α-hydroxy-9-methyl)benzylcyclohexanone, 33830-40-9.

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Acid-Catalyzed Rearrangement of 6-Methyltricyclo[4.4.0.0^{2,7}]decan-3-one

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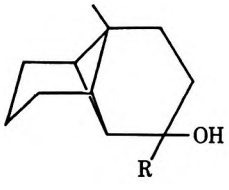
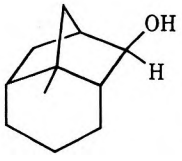
Tricyclic ketone **5** reacts in concentrated sulfuric acid to give rearrangement products **6**, **7**, **8**, and **9** in a ratio of 19:32:10:38. Tricyclic ketone **6** is produced by a mechanism involving ring expansion while compounds **7**–**9** arise by a route involving initial ring opening of ketone **5**. The structures of the rearrangement products were rigorously defined.

In the previous paper,[1] we reported that tricyclic alcohols **1** and **2** rearrange in the heterogeneous medium hexane–50% aqueous sulfuric acid to yield compounds **3** and **4**, respectively. In this paper, we describe the



1, R = H
2, R = CH_3



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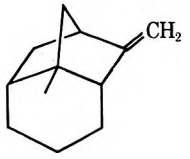

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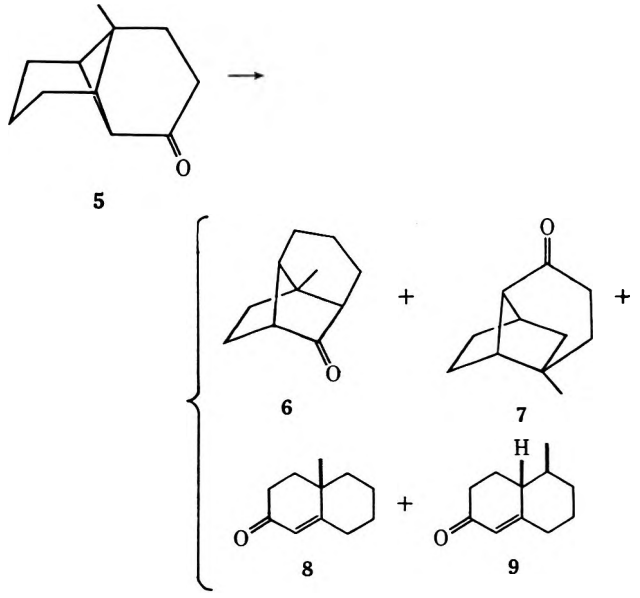
acid-catalyzed rearrangement of the parent tricyclic ketone, 6-methyltricyclo[4.4.0.0^{2,7}]decan-3-one (**5**).

When ketone **5** is dissolved in concentrated sulfuric acid and the resulting solution kept at room temperature for periods ranging from 2 hr to 2 weeks, four isomeric ketones are produced. These isomeric products, subsequently shown to have structures **6**–**9** (*vide infra*), were each isolated in a pure state by a combination of column chromatography and preparative glpc. The product analyses from several such runs are tabulated in Table I. Control experiments showed that none of the products react further when treated with concentrated sulfuric acid at 25° for 2 days.

The structures of the four products were assigned on



5

6

7

8

9

the following grounds. Ketone **8** is a known compound and was identified by comparison with an authentic specimen.[2]

Product **9** also exhibits spectral properties characteristic of an α,β-unsaturated ketone [ν_{max} 1680 and 1629 cm^{-1}, λ_{max} 238 nm (ε 12,200)]. The pmr spectrum

(1) B. E. Ratcliffe and C. H. Heathcock, *J. Org. Chem.*, **37**, 531 (1972).

(2) J. A. Marshall and W. I. Fanta, *ibid.*, **29**, 2501 (1964), and references cited therein.

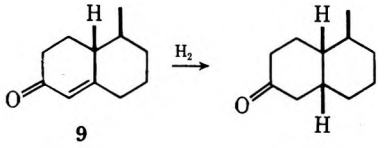
Table I

Acid-Catalyzed Rearrangement of Ketone 5

Run	Reaction time	Reaction temp, °C	Product analysis, %[a] 5	6	7	8	9	Others
1	2 hr	25	39	15	23	3	19	0
2	2 days	25	0	17	32	16	35	0
3	1 week	25	0	19	33	10	38	0
4	2 weeks	25	0	19	32	10	38	1

[a] Product analysis by glpc (6 ft × 0.25 in. 10% FFAP at 180°).

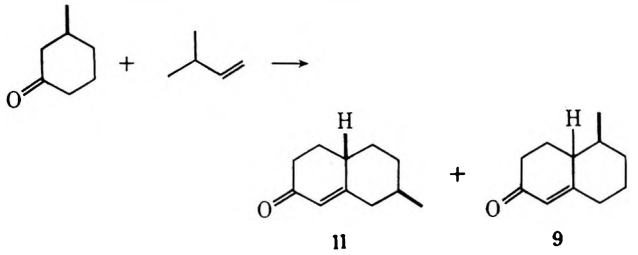
of this material contains a broad one-proton singlet at δ 5.65, attributed to a vinyl hydrogen, and a broad three-proton singlet at δ 1.07, attributed to a methyl doublet broadened by virtual coupling. Hydrogenation of **9** in ethyl acetate over palladized carbon affords a single product **10** (ν_{max} 1716 cm^{-1}), the pmr spectrum



9 **10**

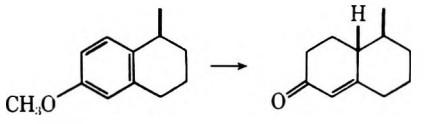
of which shows a clean methyl doublet at δ 0.98 with J = 6.0 Hz. The cis stereochemistry assigned to the ring juncture in **10** is tenuous. Augustine reports that $\Delta^{1,9}$-octal-2-one itself gives approximately equal amounts of *cis*- and *trans*-2-decalones when reduced over palladium in neutral ethanol.[3] However, 10-methyl-$\Delta^{1,9}$-octal-2-one is hydrogenated in neutral medium primarily to the cis product.[4,5] Base-catalyzed deuterium exchange studies showed that compounds **9** and **10** have six and four enolizable hydrogens, respectively.

Consideration of the above data, along with mechanistic considerations (*vide infra*), led us to propose the structure shown for compound **9**. This hypothesis was verified by independent synthesis of **9**. Robinson annelation of 3-methylcyclohexanone with methyl vinyl ketone afforded the isomeric enones **11** and **9**, along with



11 **9**

a third unidentified product in a ratio of 67:20:13, respectively. The major isomer produced in this annelation can confidently be assigned the 7-methyl structure **11**, since 3-methylcyclohexanone is known to undergo base-catalyzed condensations predominantly at C-6, rather than C-2.[6] The minor α,β-unsaturated ketone produced in the annelation reaction is therefore assigned the 5-methyl structure **9**. Both **11** and **9** are assumed to be the thermodynamically more stable isomers, with methyl equatorial, since the angular hydrogen is epimerizable under the conditions of their formation. Structure **9** was also verified by comparison of a



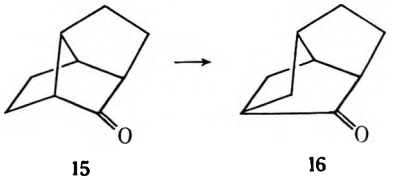
12 **9**

sample prepared from 1-methyl-5-methoxytetralin (**12**) by Birch reduction and subsequent hydrolysis of the resulting enol ether.[7]

Ketone **6** was suspected to be a cyclopentanone on the basis of its ir spectrum (ν_{max} 1750 cm^{-1}). The compound is obviously tricyclic, since it shows no vinyl proton absorption in its pmr spectrum, fails to react under catalytic hydrogenation conditions, and gives no color with tetracyanoethylene. The pmr spectrum showed an unsplit methyl resonance at δ 1.17 and a one-proton doublet at δ 2.37 (J = 4 Hz). The ketone failed to undergo deuterium exchange, indicating the absence of an enolizable α hydrogen. The structure of ketone **6** was revealed when it was treated with potassium *tert*-butoxide in *tert*-butyl alcohol at 185° for 1 week. Under these conditions, ketone **6** was transformed into ketone **13** in 84% yield. This transformation requires that compounds **6** and **13** be related by a common homoenolate, **14**. Since the structure of tricyclic ketone **13**

6 **14** **13**

has been rigorously proven,[1] the structure of ketone **6** is secure. A similar homoenolization has been reported by Nickon and coworkers[8] in the brexanone–brendanone system (**15** → **16**). In Nickon's system, as in ours, the endo-bridged isomer predominates at equilibrium.



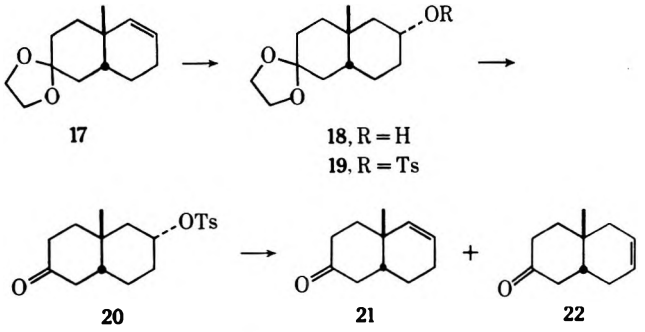
15 **16**

The fourth rearrangement product, ketone **7**, was obtained as a low-melting solid (mp 35–36°). Its ir spectrum shows that it is a cyclohexanone with an α-methylene group (ν_{max} 1706 and 1410 cm^{-1}). The ketone exchanges two hydrogens for deuterium when passed through a deuterated glpc column.[9] The pmr

(3) R. L. Augustine, *J. Org. Chem.*, **23**, 1853 (1958); **28**, 152 (1963).
(4) R. Futaki, *ibid.*, **23**, 451 (1958).
(5) F. Sondheimer and D. Rosenthal, *J. Amer. Chem. Soc.*, **80**, 3995 (1958).
(6) See, *inter alia*, (a) G. Descotes and S. Laurent, *C. R. Acad. Sci., Ser. C*, **265**, 1167 (1967); (b) G. Descotes and Y. Querou, *ibid.*, **263**, 1231 (1966).
(7) W. G. Dauben and J. I. Seeman, unpublished results. We thank Drs. Dauben and Seeman for providing us with a sample of their ketone **9** for comparison.
(8) A. Nickon, H. Kwasnik, T. Swartz, R. O. Williams, and J. B. DiGiorgio, *J. Amer. Chem. Soc.*, **87**, 1615 (1965).
(9) (a) M. Senn, W. J. Richter, and A. L. Burlingame, *ibid.*, **87**, 680 (1965); (b) G. J. Kallos and L. B. Westover, *Tetrahedron Lett.*, 1223 (1967).

spectrum contains a singlet methyl resonance at δ 1.12 and a broad three-proton envelope in the region δ 2.10–2.42, attributable to hydrogens α to the carbonyl group. Mechanistic speculation led to the postulate that this material might have the tricyclic structure indicated in structure **7**, which is also consistent with the above data. This hypothesis was confirmed by an independent synthesis of the material.

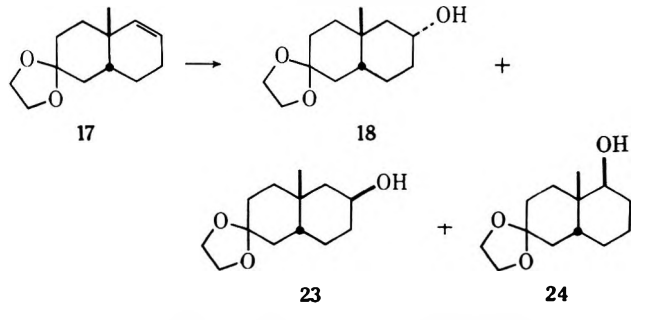
Oxymercuration–demercuration[10] of the readily available unsaturated ketal **17**[11] affords a single alcohol **18** in 90% yield. Compound **18** reacts with *p*-toluenesulfonyl chloride in pyridine to give the crystalline tosylate **19**, which is hydrolyzed to keto tosylate **20**. Evidence for both the position and configuration of the tosylate group in **20** was obtained by treating it with methylsulfinyl carbanion in dimethyl sulfoxide.[12] The product obtained from this reaction is a 60:40 mixture of octalones **21** and **22**.[13] The formation of both



17 18, R = H 19, R = Ts 20 21 22

octalones shows that the tosylate group in **20** must be at C-6 rather than C-5. Since the tosylate epimeric at C-6 is expected to undergo base-catalyzed *cyclization* (*vida infra*), the stereochemistry shown for **20** (and hence alcohol **18**) is strongly suggested.

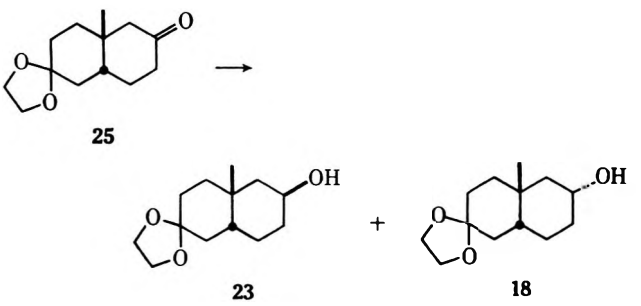
The remarkable selectivity observed in the oxymercuration of **17** is interesting, although we can offer no suitable explanation for it. Hydroboration, a reaction believed to be very sensitive to steric factors, converts olefin **17** into a mixture of three alcohols, **18**, **23**, and **24**. The highly selective hydroborating re-



17 18 23 24

agents disiamylborane[14] and 9-borabicyclo[3.3.1]-nonane[15] fail to react with compound **17**.

Oxidation of alcohol **18** with bispyridinechromium-(VI) oxide in methylene chloride[16] affords the highly crystalline keto ketal **25**, previously synthesized by



25 23 18

ketone **25** to the desired alcohol **23**, we employed various Ireland using a different route.[17] In order to convert hydride reducing agents. All reagents studied give mixtures of **23** and **18**, with the former predominating in each case (see Table II). While lithium aluminum

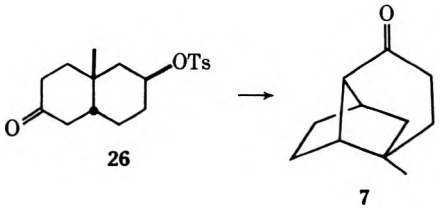
TABLE II
HYDRIDE REDUCTION OF KETO KETAL 25

Reducing agent	—Product composition, %— Alcohol 23	Alcohol 18
$LiAlH_4$	54	46
Li(*tert*-BuO)$_3$AlH	70	30
Li(*tert*-AmO)$_3$AlH[a]	72	28
Li(Et$_3$CO)$_3$AlH[a]	71	29
Lithium perhydro-9b-boraphenalylhydride[b]	68	32

[a] H. C. Brown and R. F. McFarlin, *J. Amer. Chem. Soc.*, **80**, 5372 (1958). [b] H. C. Brown and W. C. Dickason, *ibid.*, **92**, 709 (1970).

hydride gives only a sight predominance of the axial alcohol, the more bulky reagent lithium tri-*tert*-butoxyaluminum hydride yields 70% of the axial alcohol. Increasing the bulk of the reducing agent still further has little effect on the product ratio.

The 70:30 mixture of epimeric alcohols **23** and **18** was deketalized and treated with *p*-toluenesulfonyl chloride in pyridine to afford the corresponding mixture of keto tosylates. The major keto tosylate (**26**) was obtained in pure form by fractional crystallization of the mixture of epimers. When keto tosylate **26** is treated with 1 equiv of potassium *tert*-butoxide in *tert*-butyl alcohol, it is cleanly converted into the tricyclic ketone **7** (91% yield), identical in all respects with the material obtained from rearrangement of ketone **5** (*vide supra*).



26 7

With the structures of the four rearrangement products rigorously established, we may now consider possible modes for their formation. A probable mechanism for formation of the tricyclic ketone **6** is outlined in Chart I. Ring expansion of the protonated ketone gives the secondary carbonium ion **27**, which undergoes a subsequent alkyl migration to ketone **6**. As seen in Table I, approximately 20% of ketone **5** reacts by this *ring expansion* route.

(10) H. C. Brown and P. Geohagen, Jr., *J. Amer. Chem. Soc.*, **89**, 1522 (1967).
(11) C. H. Heathcock, R. A. Badger, and J. W. Patterson, Jr., *ibid.*, **89**, 4133 (1967).
(12) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1345 (1965).
(13) C. H. Heathcock and R. Ratcliffe, *J. Org. Chem.*, in press.
(14) H. C. Brown and A. W. Moerikofer, *J. Amer. Chem. Soc.*, **85**, 2063 (1963).
(15) E. F. Knights and H. C. Brown, *ibid.*, **90**, 5280, 5281 (1968).
(16) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).
(17) R. F. Church, R. E. Ireland, and D. R. Shridhar, *ibid.*, **27**, 707 (1962).

CHART I

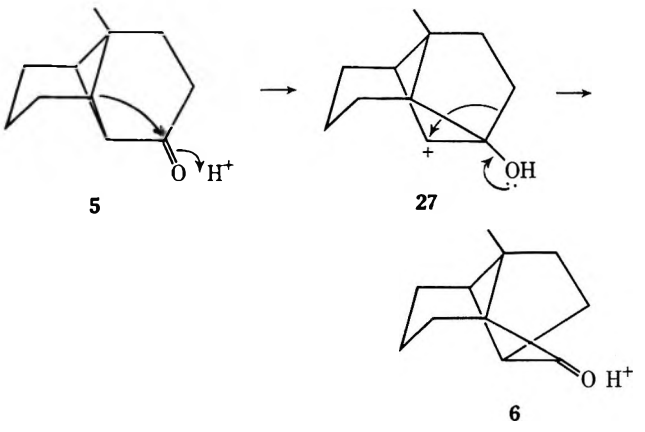
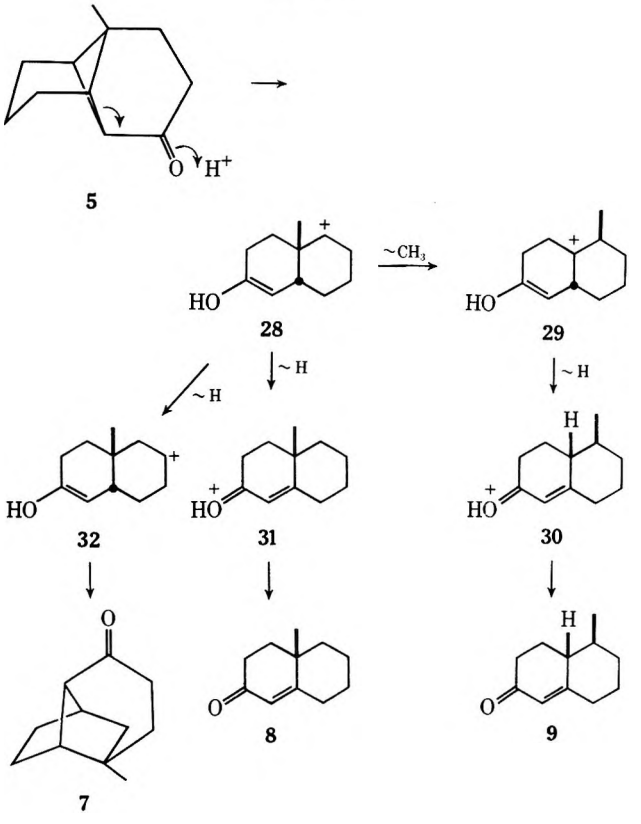


CHART II



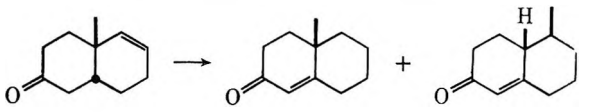
The remaining three products can be rationalized by a route involving *ring opening* of ketone **5** (Chart II). The initially formed cation **28** can undergo 1,2-methide migration to ion **29**, followed by 1,2-hydride migration to yield oxomium ion **30**.[18] Deprotonation of **30** then yields octalone **9**. Alternatively, ion **28** may undergo 1,3-hydride shift, producing oxonium ion **31**. Subsequent deprotonation of this species yields octalone **8**. When ion **28** undergoes 1,2-hydride shift to ion **32**, the positive charge may be immediately discharged by intramolecular alkylation of the enol grouping. The resulting product is tricyclic ketone **7**. Precedent for such a reaction has been provided by Stork and Grieco.[19] The scheme outlined in Chart II may well be a greatly oversimplified version of what actually transpires. We have neglected the possibility of intermediate sulfates and olefins and the keto forms of ions **28**, **29**, and **32**.

(18) Oxonium ion **30** may also be formed from **29** by a deprotonation–reprotonation mechanism.

(19) G. Stork and P. A. Grieco, *J. Amer. Chem. Soc.*, **91**, 2407 (1969).

Approximately 80% of ketone **5** apparently reacts by this ring-opening route.

In an experiment designed to shed further light on the hypothetical genesis of products **7**, **8**, and **9**, octalone **21**[11] was treated with concentrated sulfuric acid. In



this reaction, octalones **8** and **9** are produced in a ratio of 48:52. None of the tricyclic ketone **7** is formed. In this case reaction probably occurs by way of keto carbonium ions, rather than by way of enolic cations **28**, **29**, and **32**.

Experimental Section

Melting points (Pyrex capillary) and boiling points are uncorrected. Infrared spectra (ir) were recorded on Perkin-Elmer 137 and 237 spectrophotometers. Proton magnetic resonance spectra (pmr) were reported on Varian A-60 and T-60 spectrometers. Line positions are given in the δ scale, with internal tetramethylsilane as standard. The multiplicity, peak areas, coupling constants, and proton assignments are given in parentheses. Ultraviolet spectra (uv) were measured on a Perkin-Elmer 202 spectrophotometer. Consolidated 21-103c and Varian M-66 mass spectrometers provided the mass spectra. High-resolution molecular weight determinations were obtained on a Consolidated 21-110 spectrometer.

Gas liquid partition chromatography (glpc) analyses were performed on Aerograph Models 204B, A90-P, and A90-P3 instruments. Silica Gel G was used for thin layer chromatography (tlc) and Silica Gel PF_{254} for preparative tlc. Elemental analyses were performed by the Microanalytical Laboratory, operated by the Department of Chemistry, University of California, Berkeley, Calif.

Acid-Catalyzed Rearrangement of Ketone 5. A. Analytical Runs.—In a typical run, 1.64 g of ketone **5**[11] was dissolved in 4 ml of concentrated sulfuric acid. The resulting dark red solution was placed in a stoppered flask and stirred at room temperature for 1 week. At the end of this time, the solution was pured into 25 ml of water and the aqueous mixture was extracted with ether (2 × 25 ml). The ethereal solution was washed with 1 *N* NaOH (2 × 20 ml), dried, and evaporated to yield 1.40 g of product as a pale yellow oil. The product was analyzed by glpc (6 ft × 0.25 in 10% FFAP on Chromosorb W at 180°). Four volatile products were present: 19% **6** (retention time 6.9 min), 33% **7** (9.6 min), 10% **8** (12.9 min), and 38% **9** (14.1 min). Similar runs were done for periods of 2 hr, 2 days, and 2 weeks. The results are collected in Table I.

B. Characterization of Products.—To 24.23 g of tricyclic ketone **5** in a 125-ml Erlenmeyer flask was added 50 ml of concentrated sulfuric acid. The flask was stoppered and the mixture was stirred for 65 hr at room temperature. The reaction mixture was poured into 350 ml of ice–water and extracted with ether (2 × 400 ml). The ether extracts were washed with 1 *N* sodium hydroxide and water, and dried over magnesium sulfate. The ether was removed by rotary evaporation to afford 19.98 g of brown oil. The oil was chromatographed on 1.75 kg of SilicAR CC-7 to which 10% water had been added. The column was eluted with mixtures of ether in pentane ranging from 2.5% ether to 8% ether. A total of 1496 fractions of 20 ml each were collected. Every tenth fraction was monitored by both tlc and glpc (150 ft × 0.01 in. SF-96 at 145°).

Fractions 397–416 were found to contain 1.069 g of a single compound, **6**. An analytical sample, mp 81–83°, was obtained after two sublimations at 40° (0.1 mm): ir (CCl_4) 1750, 1467, 1443, 1380, 1075 cm^{-1}; pmr (CCl_4) δ 1.17 (s, 3, bridgehead Me), 2.37 (d, 1, J = 4 Hz, bridgehead H).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.28; H, 9.79.

The 2,4-dinitrophenylhydrazone melts at 132–134° after two recrystallizations from 95% ethanol.

Fractions 558–652 were found to contain 2.073 g of a single

compound, **7**, by glpc. This material was distilled through a short-path microstill to give **7** as a water-white, low-melting solid, bp 50° (0.3 mm). The analytical sample was obtained as colorless plates, mp 35–36°, after sublimation at 40° (0.65 mm): ir (CCl_4) 1706, 1475, 1450, 1410, 1375, 1284, 1257, 1078, 1029, 971 cm^{-1}; pmr (CCl_4) δ 1.12 (s, 3, bridgehead Me).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.20; H, 9.64.

The 2,4-dinitrophenylhydrazone was obtained as brilliant orange plates, mp 205–208°, after two recrystallizations from ethanol–ethyl acetate.

Anal. Calcd for $C_{17}H_{20}N_4O_4$: C, 59.29; H, 5.85; N, 16.27. Found: C, 59.15; H, 5.86; N, 16.46.

Fractions 703–1004 were found to contain 5.025 g of a 40:60 mixture of **8** and **9**. Analytical samples of **8** and **9** were obtained by preparative glpc (10 ft × 0.25 in. 4% FFAP on Chromosorb G at 180°). The ir and pmr spectra of compound **8** were identical with the corresponding spectra of the known octalone **8**.[2]

Compound **9** exhibited the following properties: ir (CCl_4) 3050, 1680, 1629, 1447, 1376, 1351, 1326, 1255, 1209, 1120, 959, 886, 862 cm^{-1}; pmr (CCl_4) δ 1.07 (broad s, 3, $W_{1/2}$ = 5 Hz, Me), 5.65 (broad s, 1, $W_{1/2}$ = 4 Hz, olefinic H); uv (95% EtOH) λ_{max} 238 mμ (ϵ_a 12,200).

Anal. Calcd for $C_{11}H_{16}O$: mol wt, 164.1201. Found: mol wt, 164.1196 (high-resolution mass spectroscopy).

Fractions 1005–1180 were composed primarily of compound **9** along with a complex mixture of more polar substances. The remaining fractions (1181–1496) contained an unidentifiable mixture of products in trace amounts.

Treatment of Ketones 6–9 with Sulfuric Acid.—In order to check the stability of the rearrangement products, each was subjected to the above reaction conditions. A typical procedure follows. A mixture of 61 mg of tricyclic ketone **6** in 1 ml of concentrated sulfuric acid was kept at room temperature for 46 hr. The solution was then poured into 10 ml of water and worked up in the normal manner. The crystalline product (51.6 mg) was shown to be unreacted ketone **6** by pmr and glpc (6 ft × 0.25 in. FFAP at 180°). Similar experiments were carried out on ketones **7**, **8**, and **9**. In each case, the starting ketone was recovered unchanged in at least 89% yield.

Base-Catalyzed Rearrangement of Tricyclic Ketone 6.—A mixture of 105 mg of tricyclic ketone **6** (0.64 mmol), 140 mg of potassium *tert*-butoxide (1.25 mmol), and 3 ml of *tert*-butyl alcohol was vacuum sealed in a thick-walled Pyrex tube and heated for 1 week at 185°.[8] The tube was opened after cooling and the contents were washed into a separatory funnel with pentane. The pentane layer was washed three times with water and dried over magnesium sulfate. The solvent was removed by rotary evaporation to afford 86.2 mg (82%) of semicrystalline solid. The spectral and chromatographic properties of this material were identical with those of tricyclic ketone **13**, prepared as previously described.[1]

Deuteration of α,β-Unsaturated Ketone 9.—The deuterated enone was obtained by preparative glpc (6 ft × 0.25 in. 10% KOD, 20% Carbowax on Chromosorb W 60/80 at 180°). The deuterated sample was analyzed for deuterium content by mass spectroscopy, which showed 2.3% $C_{11}H_{13}D_3O$, 10.8% $C_{11}H_{12}D_4O$, 34.9% $C_{11}H_{11}D_5O$, and 51.2% $C_{11}H_{10}D_6O$.

5β-Methyl-3,4,4aβ,5,6,7,8,8aβ-Octahydronaphthalen-2(1*H*)-one (10).—A mixture of 15 mg of 10% palladium on carbon and 1 ml of ethyl acetate was placed in a 10-ml round-bottom flask equipped with a magnetic stirrer and a sidearm fitted with a serum cap. The catalyst was prereduced on a low-pressure hydrogenation apparatus, and a solution of 75 mg of enone **9** in 2 ml of ethyl acetate was added by syringe. The reaction mixture was stirred at room temperature until hydrogen uptake ceased. The catalyst was filtered and washed with a few milliliters of ethyl acetate. The filtrate was evaporated at reduced pressure to afford 69 mg of ketone **10** as a colorless liquid. An analytical sample was obtained by preparative glpc (6 ft × 0.25 in. 10% FFAP at 160°); ir (CCl_4) 1716, 1449, 1376, 1263, 1224, 1155 cm^{-1}; pmr (CCl_4) δ 0.98 (d, 3, J = 6 Hz, Me).

Anal. Calcd for $C_{11}H_{18}O$: mol wt, 166.1357. Found: mol wt, 166.1353 (high-resolution mass spectroscopy).

Preparative glpc gave the deuterated ketone (6 ft × 0.25 in. 10% KOD, 20% Carbowax 20M on Chromosorb W 60/80 at 180°). Mass spectral analysis showed that the sample contained 5.9% $C_{11}H_{16}D_2O$, 17.8% $C_{11}H_{15}D_3O$, and 76.3% $C_{11}H_{14}D_4O$.

7β-Methyl-4,4aβ,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (11) and **5β-Methyl-4,4aβ,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (9).**—A solution of 22.4 g (0.2 mol) of 3-methylcyclohexanone in 70 ml of ether was placed in a 200-ml three-neck flask equipped with magnetic stirrer, condenser, and dropping funnel. The solution was cooled to 0° on an ice bath, and a solution of 2.3 g of potassium hydroxide in 7 ml of 95% ethanol was added with stirring, followed by the dropwise addition of 7.009 g (0.1 mol) of freshly distilled methyl vinyl ketone in 45 ml of ether over a period of 1.5 hr. The ice bath was removed and the reaction mixture was stirred for an additional 12 hr at room temperature. The mixture was washed with water (3 × 50 ml) and dried over magnesium sulfate. The solvent was removed by rotary evaporation, and the residue was distilled through a 4-in. Vigreux to afford 5.12 g of 3-methylcyclohexanone, bp 26–31° (1.5 mm), 6.71 g of clear liquid, bp 90–94° (0.5 mm), and 7.73 g of yellow oil, bp 144° (0.5 mm).

The fraction boiling at 90–94° (0.5 mm) was analyzed by glpc (10 ft × 0.25 in. 4% FFAP on Chromosorb G at 180°), and was found to contain three components in the ratio of 13:67:20 with retention times of 12.3, 22.5, and 24.3 min, respectively.

The major component was identified as compound **11**: ir (CCl_4) 3040, 1680, 1630, 1452, 1376, 1325, 1253, 1208, 914, 899, 854 cm^{-1}; pmr (CCl_4) δ 1.00 (unresolved d, 3, Me), 5.68 (broad s, 1, $W_{1/2}$ = 4 Hz, olefinic H).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.28; H, 9.64.

The component with a retention time of 24.3 min was identical with α,β-unsaturated ketone **9** isolated from the rearrangement of ketone **5** (*vide supra*). This material was also identical with a sample of ketone **9** prepared by another route.[7]

6α-Hydroxy-4aβ-methyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(1*H*)-one Ethylene Ketal (18).—In a 500-ml Erlenmeyer flask equipped with magnetic stirrer were placed 23.9 g (0.075 mol) of mercuric acetate, 75 ml of water, 75 ml of tetrahydrofuran, and 10.4 g (0.05 mol) of unsaturated ketal **17**.[11] The mixture was stirred at room temperature for 27 hr, during which time the bright yellow complex turned colorless. To the mixture was added 75 ml of 3 *N* sodium hydroxide, followed by 75 ml of 0.5 *N* sodium borohydride in 3 *N* sodium hydroxide. Demercuration was instantaneous. The aqueous layer was extracted with 250 ml of ether. The combined organic layers were washed with water (200 ml) and brine and dried over magnesium sulfate. The solvent was removed by rotary evaporation to afford 10.10 g of crude ketal alcohol **18** as a clear viscous oil. An analytical sample was obtained by preparative glpc (5 ft × 0.25 in. 20% Carbowax 20M at 195°): ir (CCl_4) 3400 (broad), 1445, 1350, 1089 cm^{-1}; pmr (CCl_4) δ 0.97 (s, 3, angular Me).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.87; H, 9.58.

4aβ-Methyl-6α-toluenesulfonyloxy-3,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(1*H*)-one Ethylene Ketal (19).—To a 50-ml Erlenmeyer flask equipped with a magnetic stirrer was added a solution of 2.815 g (12.45 mmol) of crude ketal alcohol **18** in 13 ml of anhydrous pyridine, followed by a solution of 2.44 g (12.8 mmol) of *p*-toluenesulfonyl chloride in 8 ml of anhydrous pyridine. The solution was allowed to stand at room temperature for 101 hr. The reaction mixture was poured onto 60 ml of ice–water and extracted with methylene chloride (25 ml, 3 × 12 ml). The combined organic extracts were washed with 10% sulfuric acid (4 × 25 ml), water (12 ml), and brine (12 ml), and dried over magnesium sulfate. The solvent was removed by rotary evaporation to afford 5.208 g (80%) of crude ketal tosylate **19** as a crystalline white solid. The crude material was recrystallized from ethyl acetate–hexane to afford 3.562 g of white crystals: mp 113.5–115.0°; ir (CCl_4) 1358, 1188, 1175, 1095, 945, 934, 880, 850, 815 cm^{-1}; pmr (CCl_4) δ 0.99 (s, 3, angular Me), 2.47 (s, 3, aryl Me), 3.85 (s, 4, ketal ethylene), 4.65 (broad m, 1, $W_{1/2}$ = 18 Hz, C-6 H), 7.55 (A_2B_2 with δ_A 7.78 and δ_B 7.34, 4, J_{AB} = 8 Hz, aryl H's).

Anal. Calcd for $C_{20}H_{28}O_5S$: C, 63.10; H, 7.42; S, 8.43. Found: C, 62.86; H, 7.02; S, 8.34.

4aβ-Methyl-3,4,4a,5,6,7,8,8aβ-octahydronaphth-6α-ol-2(1*H*)-one *p*-Toluenesulfonate (20).—A solution of 0.4 ml of concentrated sulfuric acid and 3.6 ml of water was added to a solution of 2.128 g of ketal tosylate **19** in 20 ml of acetone at 50°. The colorless solution was stirred at 50° for 45 min, cooled to room temperature, and concentrated to approximately 6 ml by rotary evaporation. The viscous liquid remaining was dissolved in ether, washed with 5% sodium bicarbonate and brine, and dried over magnesium sulfate. The solvent was removed by rotary evaporation to afford 1.834 g of semicrystalline material. Re-

crystallization from ethyl acetate–hexane yielded 1.442 g of keto tosylate **20** as white clusters: mp 77.3–78.0°; ir (CCl_4) 1718, 1600, 1366, 1190, 1180, 1100, 940, 856, 820 cm^{-1}; pmr (CCl_4) δ 1.09 (s, 3, angular Me), 2.48 (s, 3, aryl Me), 4.72 (broad m, 1, $W_{1/2}$ = 17 Hz, C-6 H), 7.57 (A_2B_2 with δ_A 7.79 and δ_B 7.34, 4, J_{AB} = 8 Hz, aryl H's).

Anal. Calcd for $C_{18}H_{24}O_4S$: C, 64.26; H, 7.19; S, 9.53. Found: C, 64.43; H, 7.06; S, 9.33.

A 0.5 *M* solution of methylsulfinyl carbanion in dimethyl sulfoxide was prepared according to the procedure of Corey.[12] This solution (4 ml) was added to a solution of 672.4 mg (2.0 mmol) of keto tosylate **20** in 4 ml of dimethyl sulfoxide under nitrogen, and the resulting solution was stirred at 60° for 2 hr. The reaction mixture was cooled, diluted with 15 ml of water, and extracted with ether (3 × 10 ml). The combined ether extracts were washed with water (10 ml) and brine (10 ml) and dried over magnesium sulfate. Removal of the solvent by rotary evaporation afforded 315.4 mg of yellow oil. Analysis by glpc (10 ft × 0.25 in. 4% FFAP on Chromosorb G at 180°) showed the product to be a 60:40 mixture of octalones **21** and **22** by coinjection with authentic samples.[13]

4aβ-Methyl-3,4,4a,5,8,8aβ-hexahydronaphthalen-2(1*H*),6-(7*H*)-dione 2-Ethylene Ketal (25).—To a 1-l. round-bottom flask equipped with magnetic stirrer and drying tube was added 42.0 g (0.531 mol) of anhydrous pyridine and 480 ml of anhydrous methylene chloride. The solution was stirred on an ice bath and 26.5 g (0.265 mol) of chromium trioxide was added all at once.[16] The orange-brown solution was stirred for 75 min, during which time the solution warmed to room temperature. A solution of 9.984 g (0.0442 mol) of crude ketal alcohol **18** dissolved in 80 ml of anhydrous methylene chloride was added, and stirring was continued for 45 min at room temperature. The methylene chloride solution was decanted from the black tarry residue and the residue was washed with ether (3 × 200 ml). The combined organics were washed with 5% sodium hydroxide (2 × 300 ml), water (300 ml), 5% hydrochloric acid (2 × 300 ml), 5% sodium bicarbonate (300 ml), and brine (300 ml) and dried over magnesium sulfate. The solvent was removed by rotary evaporation to afford 8.48 g of crude keto ketal **25** as a yellow oil. The crude product was dissolved in 5 ml of ether, and 20 ml of petroleum ether (bp 30–75°) was added. After standing in the refrigerator overnight, 6.59 g of white crystalline material was collected. Two additional crops yielded a total of 7.77 g, mp 76–78°. The analytical sample melts at 79–80° (lit.[17] mp 79.5–80.5°) after two recrystallizations from ether–petroleum ether: ir (CCl_4) 1715, 1445, 1362, 1229, 1153, 1094, 943, 872 cm^{-1}; pmr (CCl_4) δ 0.94 (s, 3, angular Me), 3.84 (s, 4, ketal ethylene).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.37; H, 8.77.

Hydride Reduction of Ketone 25. A. With Lithium Aluminum Hydride.—In a 25-ml flask equipped with magnetic stirrer, reflux condenser, and drying tube was placed a mixture of 51 mg (1.34 mmol) of lithium aluminum hydride and 10 ml of anhydrous ether. To the stirring mixture was added 100 mg (0.446 mmol) of crystalline ketone **25**. After stirring for 3 hr at room temperature, excess hydride was decomposed by the careful addition of 5% potassium hydroxide. The white precipitate was filtered and washed with ether. The filtrate was dried over magnesium sulfate and evaporated to afford 96 mg of clear liquid. The pmr spectrum showed the product to be a 46:54 mixture of the epimeric alcohols **18** and **23**.

B. With Lithium Tri-*tert*-butoxyaluminum Hydride.—To a 10-ml Erlenmeyer flask equipped with magnetic stirrer was added a solution of 100 mg (0.446 mmol) of compound **25** in 2 ml of anhydrous tetrahydrofuran. The solution was cooled in an ice bath and 200 mg (0.76 mmol) of lithium tri-*tert*-butoxyaluminum hydride in 2 ml of anhydrous tetrahydrofuran was added. The reaction mixture was stirred for 3.5 hr, during which time the mixture was allowed to warm to room temperature. Excess hydride was destroyed by careful addition of 5% potassium hydroxide. The white precipitate was filtered, and the filtrate was dried over magnesium sulfate. Evaporation of the solvent afforded 104.7 mg of clear liquid. The pmr spectrum showed the product to be a 29.5:70.5 mixture of the epimeric alcohols **18** and **23**.

C. With Lithium Tri-*tert*-amyloxyaluminum Hydride.—To a 10-ml Erlenmeyer flask equipped with magnetic stirrer was added a solution of 100 mg (0.446 mmol) of keto ketal **25** in 2 ml of anhydrous tetrahydrofuran. The solution was cooled to 0° on an ice bath and 250 mg (0.844 mmol) of lithium tri-*tert*-amyloxyaluminum hydride in 2 ml of anhydrous tetrahydrofuran was added. The reaction mixture was stirred overnight, during which time it was allowed to warm to room temperature. Excess hydride was destroyed by careful addition of 5% potassium hydroxide. The white precipitate was filtered and washed with a few milliliters of tetrahydrofuran. The filtrate was dried over magnesium sulfate and evaporated at reduced pressure to afford 87.7 mg of viscous, clear liquid. The pmr spectrum indicated the product to be a 28:72 mixture of alcohols **18** and **23**.

D. With Lithium Tri(3-ethyl-3-pentoxy)aluminum Hydride.—To a 10-ml Erlenmeyer flask equipped with magnetic stirrer was added a solution of 100 mg (0.446 mmol) of keto ketal **25** in 2 ml of anhydrous tetrahydrofuran. The solution was cooled in an ice bath and 300 mg (0.788 mmol) of lithium tri(3-ethyl-3-pentoxy)aluminum hydride in 3 ml of anhydrous tetrahydrofuran was added. The reaction mixture was stirred for 70 hr at room temperature. Excess hydride was destroyed by careful addition of 5% potassium hydroxide. The white precipitate was filtered and washed with tetrahydrofuran. The filtrate was dried over magnesium sulfate and evaporated at reduced pressure to afford 294.2 mg of yellowish liquid. The crude product was chromatographed on basic alumina (Woelm, activity I), eluting with ether–benzene mixtures. There was obtained 90.7 mg of clear liquid, whose pmr spectrum showed a 29:71 mixture of alcohols **18** and **23**.

E. With Lithium Perhydro-9b-boraphenalylhydride.—To a 50-ml three-neck flask equipped with magnetic stirrer, reflux condenser, nitrogen inlet, and rubber serum cap was added 13 ml of a 0.575 *M* (7.5 mmol) solution of lithium perhydro-9b-boraphenalylhydride in tetrahydrofuran followed by 1.12 g (5 mmol) of keto ketal **25** in 2 ml of tetrahydrofuran. The solution was stirred at room temperature in a nitrogen atmosphere for 16 hr, and 3.75 ml of 3 *N* sodium hydroxide was added followed by 3.75 ml of 30% hydrogen peroxide. The organic layer was separated and washed with 5 ml of solvent which was removed at the rotary evaporator. Addition of ether to the crude product resulted in the precipitation of a yellow solid, which was filtered. The filtrate was evaporated to afford 0.972 g of viscous liquid, whose pmr spectrum showed it to be a 32:68 mixture of alcohols **18** and **23**.

4aβ-Methyl-3,4,4a,5,6,7,8,8aβ-octahydronaphth-6β-ol-2(1*H*)-one p-Toluenesulfonate (26).—A solution of 917 mg of a 70:30 mixture of ketal alcohols **23** and **18** in 20 ml of acetone was heated to 50°. A solution of 0.4 ml of concentrated sulfuric acid in 3.6 ml of water was added and the clear solution was kept at 50° for 45 min. The reaction mixture was cooled to room temperature and concentrated to approximately 5 ml by rotary evaporation. The concentrate was dissolved in ether and washed with 5% sodium bicarbonate and brine. After drying over magnesium sulfate, the solvent was removed by rotary evaporation to afford 411.3 mg of a mixture of keto alcohols. This material was dissolved in 2.5 ml of anhydrous pyridine and added to a solution of 475 mg of *p*-toluenesulfonyl chloride. The mixture was stirred to make it homogeneous and allowed to stand for 134 hr at room temperature. The reaction mixture was poured into 15 ml of water and extracted with chloroform (10 ml, 3 × 5 ml). The combined organic extracts were washed with 10% sulfuric acid (4 × 5 ml), water (5 ml), and brine (5 ml), and dried over magnesium sulfate. Evaporation of the solvent at reduced pressure afforded 576 mg of viscous liquid. This material was induced to crystallize from ethyl acetate–hexane to yield 203 mg of white crystalline keto tosylate **26**. An analytical sample was obtained by recrystallization from ethyl acetate–hexane to give white clusters: mp 105–107°; ir (CCl_4) 1718, 1603, 1453, 1364, 1190, 1178, 1099, 958, 950, 919, 857 cm^{-1}; pmr (CCl_4) δ 1.26 (s, 3, angular Me), 2.45 (s, 3, aryl Me), 4.57 (broad m, 1, $W_{1/2}$ = 18 Hz, C-6 H), 7.51 (A_2B_2 with δ_A 7.72 and δ_B 7.31, 4, J_{AB} = 8.5 Hz, aryl H's).

Anal. Calcd for $C_{18}H_{24}O_4S$: C, 64.26; H, 7.19; S, 9.53. Found: C, 64.07; H, 6.99; S, 9.40.

6-Methyltricyclo[4.4.0.0^{2,8}]decan-3-one (7).—To a solution of 28.1 mg (0.25 mmol) of potassium *tert*-butoxide in 1 ml of anhydrous *tert*-butyl alcohol was added 90 mg (0.268 mmol) of crystalline keto tosylate **26**. The mixture was refluxed under nitrogen for 3 hr and poured into 3 ml of ice-cold water. The resulting mixture was extracted with ether (2 × 2 ml). The combined ether extracts were washed with water (3 × 1 ml) and dried over magnesium sulfate. The solvent was removed by rotary evaporation to afford 40 mg (91%) of crude tricyclic ketone **7** as an orange-tinted semisolid. An analytical sample was obtained

by preparative glpc (10 ft × 0.25 in. 10% SE-30 at 170°). The spectral properties of this material were identical in all respects to those of the material isolated from the acid-catalyzed rearrangement of tricyclic ketone **5** (*vide supra*).

Acid-Catalyzed Rearrangement of Octalone 21.—To 821.4 mg of octalone **21**[11] in a 10-ml Erlenmeyer flask was added 2 ml of concentrated sulfuric acid. The flask was stoppered and the brown mixture was stirred for 2 days at room temperature. The mixture was poured into 15 ml of ice–water and extracted with ether (2 × 15 ml). The combined extracts were washed with 20 ml of 1 *N* sodium hydroxide and dried over magnesium sulfate. The solvent was evaporated to afford 646.8 mg of yellow oil. Glpc analysis of the product (6 ft × 0.25 in. 10% FFAP at 180°) revealed the presence of two components in a ratio of 48:52. The two components were identified as the α,β-unsaturated ketones **8** and **9**, respectively, by comparison of their spectra with those of authentic samples.

Registry No.—**5**, 17159-66-9; **6**, 18503-74-7; **6** 2,4-DNP, 18503-75-8; **7**, 33830-72-7; **7** 2,4-DNP, 33830-73-8; **9**, 33835-42-6; **10**, 33835-43-7; **11**, 33835-44-8; **18**, 25826-87-3; **19**, 33835-46-0; **20**, 33835-47-1; **25**, 33835-48-2; **26**, 33835-49-3.

Acknowledgments.—We thank the National Science Foundation and the Alfred P. Sloan Foundation for financial support.

Strained Ring Systems. XI.[1a] The Synthesis of Benzobicyclo[2.2.0]hexa-2,5-diene, Benzobicyclo[2.2.0]hex-2-ene, and Benzobicyclo[2.2.0]hex-5-en-*exo*-2-ol[1b]

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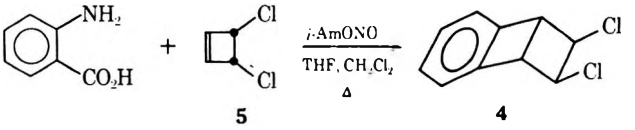
This paper describes the cycloaddition of benzyne with *cis*-3,4-dichlorocyclobutene to give *exo,cis*-5,6-dichlorobenzobicyclo[2.2.0]hex-2-ene (**4**), the disodium–phenanthrene dechlorination of **4** to benzobicyclo[2.2.0]-hexa-2,5-diene (**2**), the diimide reduction of **2** to benzobicyclo[2.2.0]hex-2-ene (**3**), and the hydroboration of **2** to benzobicyclo[2.2.0]hex-5-en-*exo*-2-ol (**8**). Some of the spectral features of these compounds are discussed.

When Dewar in 1867[2] reported his results from the oxidation of phenol, he suggested the use of a model by which he could construct the various structural isomers of a given molecular formula. For the formula C_6H_6, one of the structures written was that of bicyclo[2.2.0]-hexa-2,5-diene (**1**), which has become known as "Dewar benzene." Nearly 100 years later, van Tamelen and Pappas[3] reported the successful synthesis of **1**. Since that report various syntheses and studies of the chemistry of derivatives of **1** have been reported.

In our continuing program of the chemistry of molecules incorporating the [2.2.0] system, we felt that it would be most useful to develop a synthesis of benzobicyclo[2.2.0]hexa-1,5-diene ("hemi Dewar naphthalene")[4] (**2**) which might also be applicable to the preparation of 1-substituted derivatives of benzobicyclo[2.2.0]hex-2-ene (**3**). Since **2** should be convertible to 5-substituted derivatives of **3**, this approach would make available this set of compounds for further study. Such a synthetic approach has been achieved and is the subject of this paper.

Synthesis.—Conceptually, the approach was to prepare *cis*-5,6-dichlorobenzobicyclo[2.2.0]hex-2-ene (**4**) by the cycloaddition of benzyne and *cis*-3,4-dichlorocyclobutene[7] (**5**) and then to seek methods for dechlorination of **4** to **2**. Two methods were carried out for the cycloaddition reaction. One involved the *in situ* generation of the benzyne precursor and benzyne itself;[8a] only 0.1% of **4** was obtained. The second method involved isolation of the benzyne precursor, benzenediazonium-2-carboxylate (**6**),[8b] and allowing it to decompose thermally in the presence of **5**. Yields of **4** ranging from 2.4 to 11.3% were obtained depending on the ratio of **5**:**6** used. The impurities in the crude reaction mixture appeared to be largely aromatic from the nmr spectrum; one of these was benzoic acid. Chromatography on basic, activity I alumina and elution with carbon tetrachloride gave quite pure **4** in the first few fractions. The infrared spectrum of **4** was fairly simple, indicating a high degree of symmetry in the tricyclic structure.



5 **4**

The nmr spectrum (CCl_4, internal TMS) of **4** exhibited absorptions centered at τ 2.80 (m, 4), 5.55 (m, J = 0.9 Hz, 2), and 5.92 (m, J = 0.8 Hz, 2). The aromatic hydrogens were assigned to the finely split multiplet at τ 2.80 which is only 0.2 ppm lower field than the center of the aromatic proton multiplet of benzocyclobutene (τ 3.01).[9] Irrespective of how we wish to rationalize the assignments[10] of the latter two absorptions (C_1, C_4 bridgehead *vs.* C_5, C_6 methine protons), the fact that the coupling constants are so small

(1) (a) Paper X: R. N. McDonald and E. P. Lyznicki, *J. Amer. Chem. Soc.*, **93**, 5920 (1971). (b) Part of this research was communicated in R. N. McDonald and D. G. Frickey, *ibid.*, **90**, 5315 (1968). (c) Taken from the M.S. thesis of D. G. Frickey, 1968, and the Ph.D. thesis of G. M. Muschik, 1972.

(2) (a) J. Dewar, *Proc. Roy. Soc. Edinburgh*, 84 (1866); (b) W. Baker, *Chem. Brit.*, **1**, 191 (1965), discusses Dewar's paper, and some of the efforts to synthesize **1** and its various derivatives.

(3) E. E. van Tamelen and S. P. Pappas, *J. Amer. Chem. Soc.*, **85**, 3297 (1963).

(4) We are aware of only two other literature entries into this family of compounds which incorporate two of the classically considered structures of benzene fused into a single molecule; one is a bridged "Dewar anthracene" reported by Applequist and Searle,[5a] and the second is a report of the 1,2-dimethyl and 1,2,3,4-tetramethyl derivatives of **2**.[5b] The preparation of "hemi Dewar biphenyl," a compound in which the moieties are joined but not fused, has been described by Burt and Pettit.[6]

(5) (a) D. E. Applequist and R. Searle, *J. Amer. Chem. Soc.*, **86**, 1389 (1964); (b) D. T. Carty, *Tetrahedron Lett.*, 4753 (1969).

(6) G. D. Burt and R. Pettit, *Chem. Commun.*, 517 (1965).

(7) M. Avram, I. Dinulescu, M. Elian, M. Farcasiu, E. Marica, G. Mateescu, and C. D. Nenitzescu, *Chem. Ber.*, **97**, 372 (1964).

(8) (a) L. Friedman and F. M. Logullo, *J. Amer. Chem. Soc.*, **85**, 1549 (1963); (b) M. Stiles, R. G. Miller, and U. Burkhardt, *ibid.*, **85**, 1792 (1963).

(9) G. Fraenkel, Y. Asahi, M. J. Mitchell, and M. P. Cava, *Tetrahedron*, **20**, 1179 (1965).

(10) See S. J. Cristol and G. W. Nachtigall, *J. Org. Chem.*, **32**, 3738 (1967), for the assigned nmr spectrum of the related *exo,cis*-5,6-dichlorobicyclo-[2.2.1]hept-2-ene.

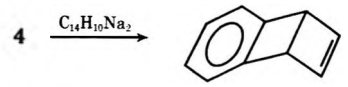
requires the cis,exo relationship of the chlorines in **4**.[11]

The mass spectrum[12] of **4** was correct for a dichloride with the $M^{+}\cdot$, $M^{+}\cdot + 2$, $M^{+}\cdot + 4$ peaks in a ratio of 1:0.625:0.25, which is well within experimental error of the expected ratio since the intensities of these peaks are very small. The base peak is *m/e* 128 and could correspond to the radical cations of naphthalene or "hemi Dewar naphthalene."

Chemical proof of the gross structure of **4** was given by its dehydrohalogenation with potassium *tert*-butylate in *tert*-butyl alcohol to 2-chloronaphthalene in 45% yield. This product was characterized by comparison of its nmr spectrum with that of authentic material.

The next step in this investigation was to examine methods for converting **4** into **2**. Reaction of **4** with methyllithium[13] did not take place and with sodium in 1,2-dimethoxyethane formation of only a small amount of **2** was observed. Treatment of **4** with lithium or sodium in *tert*-butyl alcohol and tetrahydrofuran[14] produced trace to small amounts of **2** along with varying amounts of tetralin, 1,4-dihydronaphthalene, and naphthalene, and, in the case using lithium, a small amount of benzobicyclo[2.2.0]hex-2-ene (**3**).[15]

Finally, it was found that disodium–phenanthrene,[16] a mild dehalogenating reagent, effected the dechlorination of **4** to **2** in 34% yield.[17]



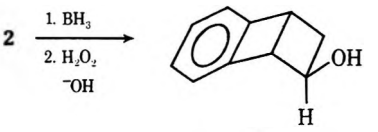
2

The nmr spectrum of **2** (the samples always contain trace to small amounts of naphthalene) exhibited three finely split multiplets at τ 2.95 (aromatic), 3.43 (olefinic), and 5.58 (bridgehead); this spectrum is reproduced in ref 1b. The chemical shift of the olefinic protons is virtually identical with the values reported for the analogous protons (τ 3.45) of bicyclo[2.2.0]hexa-2,5-diene (**1**)[3] and (τ 3.43) benzobicyclo[2.2.1]hepta-2,5-diene (**7**).[10] The bridgehead protons of **2** absorbed 0.58 ppm downfield from those of **1**[3] (τ 6.16) and over 0.8 ppm downfield from those in **7** (τ 6.41, neat).[10]

The ultraviolet spectrum of **2** was not sufficiently different from that of benzocyclobutene[18] to warrant postulation of homoconjugation of the olefinic double bond with the aromatic ring

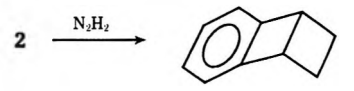
As was previously mentioned, **2** rearranges to naphthalene. The rate constant for this rearrangement was determined in carbon tetrachloride at 38 ± 0.2°, the ambient probe temperature of the nmr spectrometer. A half-life of 3.96 hr and a rate constant of $(4.85 \pm 0.48) \times 10^{-5}$ sec^{-1} were determined for this rearrangement under these conditions.

Hydroboration of **2** followed by reaction of the intermediate borane with basic hydrogen peroxide produced benzobicyclo[2.2.0]hex-5-en-*exo*-2-ol (**8**) in 15% yield (based on **4**). The exo configuration of the 2-hydroxy substituent in **8** is argued for by analogy with the specific exo hydroboration of bicyclo[2.2.0]hex-2-ene[19] and other bicyclic olefins, and the results of spin decoupling of the nmr spectrum of **8**.[20]



8

To further characterize **2**, it was reduced with diimide to **3**.[17] Attempted glpc of **3** led to rearrangement, with



3

1,2-dihydronaphthalene and naphthalene as the only observed products. The mass spectrum[22] of **3** showed a large $M^{+}\cdot$ ion (*m/e* 120, relative abundance 79%) with the $M^{+}\cdot - 1$ peak as the base peak. This may involve cleavage of the C_1–C_4 bridge bond with loss of a hydrogen atom to produce benzylic cation **9**. Further loss of a hydrogen atom then leads to *m/e* 128 (relative abundance 72%), the naphthalene or **2** cation radical. The second major process appears to be the loss of $\cdot CH_3$ to an ion *m/e* 115 (relative abundance 74%). A third path of electron impact fragmentation is the loss of ethylene from $M^{+}\cdot$, the product of which may be **10** (*m/e* 102, relative abundance 10%).

9 **10**

The nmr spectrum of **3** (reproduced in ref 1b) consists of an A_2B_2 multiplet for the aromatic protons centered at τ 2.93, a multiplet centered at τ 6.19 for the bridgehead protons, and a complex multiplet between τ 7.33 and 8.28 attributed to the methylene protons. The ultraviolet spectrum of **3** showed that the three large absorptions were shifted to somewhat lower wavelengths than those of **2** and gave a reasonable correspondence to those of benzocyclobutene.[18]

(11) Cis vicinal coupling constants in four-membered rings are large (4–10 Hz); see F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, p 362.

(12) We thank Dr. R. W. Kiser, University of Kentucky, for determination of this mass spectrum on an RMU-6E mass spectrometer.

(13) G. Schroder and T. Martini, *Angew. Chem., Int. Ed. Engl.*, **6**, 806 (1967), reported a 70% yield of 2-chloro-3-fluorobicyclo[2.2.0]hexa-2,5-diene from the reaction of 5,5-dichloro-6,6-difluorobicyclo[2.2.0]hex-2-ene and methyllithium.

(14) P. G. Gassman and P. G. Pape, *J. Org. Chem.*, **29**, 160 (1964).

(15) The components were shown to be present from the nmr spectra of chromatographic fractions of the mixtures.

(16) E. Vogle, H. Kiefer, and W. R. Roth, *Angew. Chem., Int. Ed. Engl.*, **3**, 442 (1964), reported the use of this reagent in a debromination step to produce bicyclo[2.2.0]octa-2,4,7-triene.

(17) This is a minimum yield. The yield of **2** used in a diimide reduction to **3** was 58% assuming a 90% yield in the reduction step.

(18) M. P. Cava and D. R. Napier, *J. Amer. Chem. Soc.*, **80**, 2255 (1958).

(19) R. N. McDonald and C. E. Reineke, *J. Org. Chem.*, **32**, 1878 (1967).

(20) Saturating in the methylene proton (xH_3 and nH_3) region (τ 7.6–7.85) the original methine (nH_3) simplified to a broad singlet. The residual coupling was between H_1 and nH_2 and must be less than J = 1 Hz, which establishes the hydroxyl group as exo.[11,21] Saturation in the bridgehead proton (H_1 and H_4) region simplifies the methylene (xH_3 and nH_3) multiplet to a complex doublet due to the remaining germinal coupling, $J_{nH_2} - J_{xH_2}$, a chemical shift difference in xH_3 and nH_3, and cis ($J_{nH_2} - J_{nH_3}$) and trans ($J_{nH_2} - J_{xH_3}$) vicinal couplings. The triplet observed for nH_2 sharpened by saturating at the bridgehead proton region. n and x refer to endo and exo, respectively.

(21) (a) K. B. Wiberg, V. Z. Williams, and L. E. Friedrich, *J. Amer. Chem. Soc.*, **90**, 5338 (1968); (b) K. B. Wiberg and D. E. Barth, *ibid.*, **91**, 5124 (1969).

(22) We thank Dr. R. G. Cooks for determination of this mass spectrum on an MS-9 mass spectrometer.

Experimental Section[23]

Benzenediazonium-2-carboxylate.—This compound was prepared according to the published procedure.[8b] Yields of 33–61% of brown to light buff needles were obtained. The infrared spectrum compared well to that reported.[8b] *Caution:* This compound is explosive when subjected to friction, especially when scraped on hard surfaces.

***exo,cis*-5,6-Dichlorobenzobicyclo[2.2.0]hex-2-ene (4).**—To a solution of 13.2 g (107 mmol) of *cis*-3,4-dichlorocyclobutene[7] in 100 ml of dioxane (distilled from sodium) was added 3.14 g (21.2 mmol) of freshly prepared benzendiazonium-2-carboxylate. The resultant slurry was magnetically stirred at 48–52° under nitrogen until the mixture became homogeneous (3.25–4.5 hr depending on the purity of the benzyne precursor). The solution was dark brown at this point. The dioxane and the *cis*-3,4-dichlorocyclobutene were removed under vacuum using a 33-cm Vigreux column with a maximum pot temperature of 70°, leaving a dark brown viscous residue. This residue was dissolved in about 100 ml of ether and filtered to give a colored solution. The ether was evaporated in a molecular still, and the product was sublimed at room temperature and 0.05 mm from the residue as a white crystalline solid mixed with a light yellow oil. The oil was separated from the solid by rubbing the mixture on a piece of absorbent paper. This afforded 0.48 g (11.3% yield) of crude product. Further purification was effected by subliming half of the total yield at room temperature and 0.05 mm, cleaning the cold finger and continuing the sublimation. The second half of the sublimation was the purer sample (mp ~ 70–79°), which was purified further by repeated sublimations.

The first half was impure and was purified by column chromatography using neutral, activity I Woelm alumina with carbon tetrachloride as an eluent with a fairly fast elution rate. The first few fractions contained the purest product, mp 60–79°, from the chromatography. This was purified further by repeated sublimations. The melting point of the product was 79–79.5° (sealed tube). The nmr, infrared, mass, and ultraviolet [263 nm (log ε 3.19), 267 (shoulder) (3.23), 269 (3.42), and 275.3 (3.44) in cyclohexane] spectra all agreed with the assigned structure.

Anal. Calcd for $C_{10}H_8Cl_2$: C, 60.35; H, 4.02. Found: C, 60.39; H, 4.14.

In several runs of this preparation, various ratios of the *cis*-3,4-dichlorocyclobutene to benzenediazonium-2-carboxylate were used. Table I is a table of these ratios and their respective yields.

TABLE I

Cyclobutene: diazonium salt	Yield of 4, %
3.7:1	7.3
5.5:1	4.5
8.0:1	10.4
4.0:1	10.0
5.0:1	11.3
12.5:1	8.9
1.5:1	2.4

These yields are based on the product sublimed from the crude product mixture with the benzenediazonium-2-carboxylate as the limiting reagent as described in the above procedure.

Dehydrochlorination of *exo,cis*-5,6-Dichlorobenzobicyclo[2.2.0]hex-2-ene.—4 (30 mg, 0.15 mmol) was dissolved in 4.5 ml of *tert*-butyl alcohol (distilled from sodium). To this was added 24 mg (0.6 mg-atom) of potassium and the mixture was heated under reflux overnight. Water (25 ml) was then added and the mixture was extracted with three 25-ml portions of pentane. The pentane extracts were washed with three 100-ml portions of water, dried ($MgSO_4$), and distilled to near dryness. The rest of the solvent was evaporated on a rotary evaporator to give 11 mg (45% yield) of crude 2-chloronaphthalene, mp 35–58° (lit.[24] mp 58°). The nmr spectrum of the product was identical with that of an authentic sample.

Benzobicyclo[2.2.0]hexa-2,5-diene (2).—To a magnetically stirred solution of 2.021 g (11.79 mmol) of phenanthrene in 10 ml of freshly distilled glyme (distilled from calcium hydride and then from lithium aluminum hydride) in a 25-ml, dry, two-necked flask fitted with a rubber septum and a gas inlet was added 0.700 g (30.4 mg-atoms) of sodium at ice bath temperature. (The sodium was cut immediately prior to addition and added quickly so as to present a clean surface to the phenanthrene solution.) After a few minutes of stirring under nitrogen, the solution became very dark green. Thirty minutes was allowed for the reaction of the sodium with the phenanthrene.

The green solution was then recovered from the flask by means of a syringe and charged into a solution of 0.782 g (3.93 mmol) of **4** (75–90% pure) in 10 ml of anhydrous glyme under nitrogen at room temperature in a 50-ml two-necked flask fitted as above. The first few drops were decolorized and a white precipitate formed immediately. After 30 min of stirring under nitrogen, the mixture became brown and never lightened much more during the 1.25-hr reaction time.

The reaction mixture was dissolved in 100 ml of ether, which was washed with four 50-ml protions of water and dried ($MgSO_4$) in the freezer. Evaporation on a rotary evaorator to near dryness gave a yellow, solid residue. Any residual ether or glyme was evaporated by means of an oil pump and collected in a Dry Ice cooled trap. The product was distilled using a trap-to-trap apparatus at room temperature and 0.1–0.2 mm pressure and collected in a trap cooled in liquid nitrogen. The length of time of distillation was determined by stopping when a little of the starting material began to sublime onto the inside of the upper portion of the vacuum adaptor used for the distillation. The yield of the product as a clear, colorless liquid was 171 mg (34%). The unreacted starting material was recovered by subliming about one-fourth to one-third of the residual solid from the distillation and chromatographing the sublimate on basic, activity I alumina with carbon tetrachloride as the eluent.

The nmr and ultraviolet [257.8 nm (shoulder) (log ε 2.75), 263.4 (2.97), 270 (3.12), 276.5 (3.15), 284.5 (2.37), 287 (2.32) in cyclohexane containing *ca.* 5.6% naphthalene impurity] spectra were in agreement with the assigned structure of **2**.

Determination of the Kinetics of the Isomerization of 2 to Naphthalene.—A sample of 5–10 mg of **2** was dissolved in 0.2 ml of carbon tetrachloride (distilled from phosphorus pentoxide) to give a 0.17–0.39 *M* solution. Using a capillary tube containing a 10% solution of methylene chloride in carbon tetrachloride as a standard, the amount of **2** present at various times was determined by integration. The nmr spectral absorption corresponding to the τ 3.42 absorption of **2** and the methylene chloride singlet were integrated and a ratio of the areas was obtained. The temperature at which the study was done was 38 ± 0.2°, the ambient probe temperature.

Benzobicyclo[2.2.0]hex-2-ene (3).—A 250-mg (1.26 mmol) sample of dichloride **4** was dechlorinated to **2** using the disodium–phenanthrene complex. Two trap-to-trap distillation fractions were obtained which contain **2** with no apparent naphthalene present. These fractions were dissolved in 5 ml of dry methanol and combined with a yellow, methanolic slurry of dipotassium azodicarboxylate [prepared from 0.630 g (5.43 mmol) of azodicarbonamide[25]] with stirring under nitrogen. To this was slowly added a solution of 0.90 ml of glacial acetic acid dissolved in 5 ml of dry methanol over a 2-hr period at room temperature. The yellow slurry changed to white after a portion of the acid had been added. After stirring under nitrogen for an additional 5 hr, the reaction mixture was transferred to a separatory funnel with 150 ml of ether. The ether layer was separated, washed with eight 60-ml portions of water and 10 ml of saturated, aqueous sodium bicarbonate solution, and dried ($MgSO_4$) in the refrigerator overnight. Evaporation of the ether left a yellow, liquid residue which was trap-to-trap distilled to give 85 mg of **3**, bp 25° (0.5–0.8 mm). This represents a 52% overall yield of **3** from **4**. The nmr and ultraviolet [262 nm (OD_{max} 0.94), 268 (1.17), 274 (1.28), and 285 (0.89)][26] spectra were in agreement with the assigned structure.

(23) All melting points were determined on a Kofler hot stage and are corrected. Boiling points are uncorrected. Infrared and ultraviolet spectra were determined on a P-E 137 and Cary 11 spectrophotometer, respectively, while nmr spectra were obtained on a Varian A-60 spectrometer. Gas chromatographic analyses were performed using a F & M Model 500 temperature-programmed gas chromatograph. Microanalyses were done by Galbraith Laboratories.

(24) F. D. Chattaway and W. H. Lewis, *J. Chem. Soc.*, 875 (1894).

(25) J. Thiele, *Justus Liebigs Ann. Chem.*, **271**, 127 (1892).

(26) Extinction coefficients were not determined for this spectrum due to an unknown degree of contamination by naphthalene and binder from tlc from another preparation.

Another preparation of **3** produced enough pure compound by column chromatography for elemental analysis.

Anal. Calcd for $C_{10}H_{10}$: C, 92.26; H, 7.74. Found: C, 92.09; H, 7.74.

Benzobicyclo[2.2.0]hex-5-en-*exo*-2-ol (8).—**4** (150 mg) was converted to **2** as described above. Olefin **2** was immediately transferred to a reaction vessel containing 1 ml of tetrahydrofuran (distilled from $LiAlH_4$) at 5–10°. To this was added 0.45 ml of a 0.45 *M* diborane solution in tetrahydrofuran. After stirring for 1 hr, water was added dropwise to destroy excess diborane followed by 0.1 ml of 3 *N* aqueous sodium hydroxide and 0.1 ml of 30% hydrogen peroxide. Stirring was continued for 1 hr. The reaction mixture was extracted with 20 ml of ether, which was separated and washed with four 5-ml portions of saturated, aqueous brine. The organic layer was dried ($MgSO_4$) at 0°, the ether was removed on a rotatory evaporator, and the liquid residue was chromatographed on activity II, basic alumina to give 17 mg (15% based on **4**) of **8**: ir (neat) 3260, 2950, 1460, 1060, and 745 cm^{-1}; nmr (CCl_4, internal TMS) τ 2.85 (m center, aromatic A_2B_2, 4), 5.75 (t center, C_2H, 1), 6.15 (m center, bridgehead H's, 2), 6.87 (s, OH, 1), and 7.6–7.85 (m, CH_2, 2).

Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.90. Found: C, C, 81.98; H, 6.81.

Registry No.—**2**, 20847-82-9; **3**, 20847-83-0; **4**, 20902-25-4; **8**, 33905-59-8.

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Synthesis of Angularly Substituted Tetrahydro- and Hexahydrofluorenes[1]

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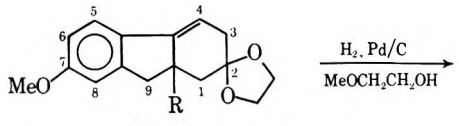
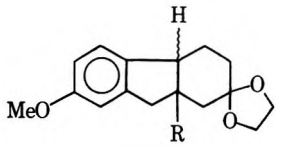
A series of 7-methoxy-2,2-ethylenedioxy-1,2,3,9a-tetrahydrofluorenes has been synthesized in which the 9a substituent has been transformed from COOEt into CHO, CHNOH, COOLi, COONa, $CONH_2$, CN, and COMe as well as into the previously reported groups COOMe, CH_2OH, and COOH. For each substituent the cis and trans compounds resulting from olefin reduction have been synthesized by routes which establish their stereochemistry. The influence of the stereochemistry at C-4a on the course of reactions at the group attached at C-9a is discussed.

In the hydrogenation of olefins over heterogeneous catalysts, the stereochemistry of reduction has been found to be influenced not only by the bulk of neighboring functional groups but by attractive interactions between certain of these groups and the catalyst surface.[3] These interactions, in contrast to steric effects, are responsible for addition of hydrogen cis with respect to the group involved. Our study of this phenomenon[3] required us to synthesize a series of compounds **1u**, in which the angular group R represented a



1u



1c = cis; **1t** = trans

variety of common functional groups, as well as requiring us to prepare authentic samples of the corresponding cis (**1c**) and trans (**1t**) reduction products.

We report here these syntheses, which were accomplished by transformations of the unsaturated carboethoxy compound (**2u**) and which illustrate reactivities and limitations in a system which is both severely crowded and acid sensitive. The results are instructive as to the relative usefulness in such an environment of a number of the existing methods for functional group transformation.

The only cases for which we had already made entire sets consisting of all three compounds (**u**, **c**, and **t**) for a given functional group were carbomethoxy (**3**) and hydroxymethyl (**4**). Since the stereochemistry of each of these materials was unequivocally known,[3] they were in practice the starting or reference points for our synthetic sequences. As these sequences in many instances parallelled each other for our three series of compounds (Schemes I–III) we shall usually discuss the transformations in the unsaturated series as being typical of all three.

We had synthesized the previously reported cis aldehyde (and established its stereochemistry)[4] by oxidation of the *cis*-hydroxymethyl compound **4c** with CrO_3 in pyridine.[5] The same procedure was successful for preparation of **5u** and **5t**; however, yields were consistently poor and we found that greatly improved yields for the entire aldehyde set could be obtained with the procedure employing dicyclohexylcarbodiimide and dimethyl sulfoxide.[6] Treatment of the aldehyde **5u** with hydroxylamine in ethanol proceeded smoothly to give the oxime **6u**.[7]

The unsaturated carboxylic acid **7u** had been produced as previously described[3] from the corresponding ester by saponification. The trans acid could also be obtained by saponification, albeit under more drastic conditions than were required for **2u**, and the stereochemistry of **7t** was thus related unequivocally to the trans series. As none of the reduction methods tried on the unsaturated ester **3u** gave appreciable quantities of cis ester, we could not prepare the cis acid by an analogous saponification. However, metal–ammonia reduction of the acid **7u** provided **7c** in good yield and

(1) Abstracted in part from the Ph.D. thesis of R. E. N.
(2) NASA Predoctoral Trainee, 1966–1967.
(3) H. W. Thompson, *J. Org. Chem.*, **36**, 2577 (1971).
(4) H. W. Thompson, *ibid.*, **32**, 3712 (1967).
(5) J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, **45**, 331 (1962).
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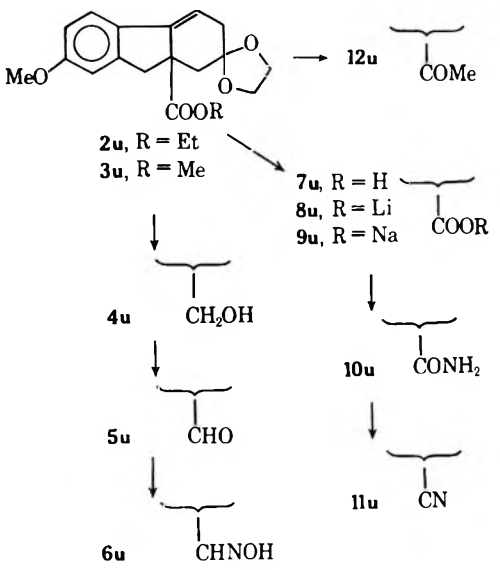
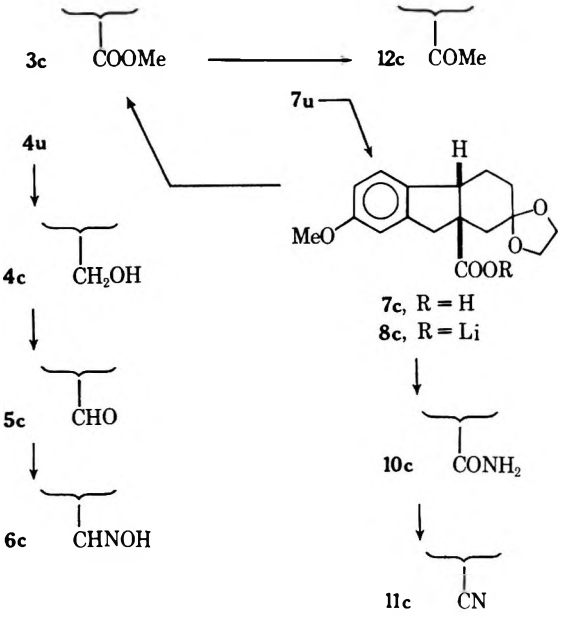
(7) The same procedure was used to obtain the cis and trans isomers.

SCHEME I
UNSATURATED SERIES



SCHEME II
CIS SERIES



the methyl ester was in turn prepared from **7c** by treatment with diazomethane.[3]

The acid **7u**, in addition to being the starting point for the above compounds and for the nitrogen-bearing compounds of the unsaturated series (Scheme I), was converted to its sodium and lithium carboxylates by careful treatment with exactly or slightly less than equivalent amounts of the corresponding metal hydrides, followed by removal of excess **7u** by trituration with hot benzene until the ir spectrum showed complete loss of carbonyl stretching absorption.[7]

In order to prepare the amide **10u** we attempted ester ammonolysis under a variety of conditions, ranging from anhydrous ethanolic ammonia (no reaction) to potassium amide in liquid ammonia (very poor yields). Of several procedures involving conversion of carboxylic acid salts into reactive intermediates,[8,9] the most successful was treatment of the lithium carboxylate **8u** with oxalyl chloride in pyridine solution,[9] followed by reaction with liquid ammonia; this provided **10u**[7] in a yield of 52%. Dehydration of the carboxamide to the corresponding nitrile (**11u**) proceeded readily in THF–pyridine on treatment with thionyl chloride.[7,10]

Our attempts to convert the carboxylic acid to the acetyl compound by direct methylation of the lithium salt **8u** with methyllithium[11] resulted in poor yields of **12u** and isolation of mixtures either rich in starting material or in tertiary alcohol. Alternate pathways involving treatment of the aldehyde **5u** with methyl Grignard followed by oxidation,[6] and treatment of the acid chloride with cadmium reagent, proved equally unpromising. The sequence which proved successful for the synthesis of **12u** and **12c** was the condensation of DMSO anion with an ester followed by reductive cleavage of the α carbon–sulfur bond with aluminum amalgam.[12] However, this was not successful for synthesis of the *trans*-methyl ketone from **2t**, the only ketonic product isolated being, not **12t**, but **12c**, evidently due to removal of the tertiary benzylic proton under the very strongly basic reaction conditions. This and the subsequently described isomerization in the methyl set of compounds provide additional evidence for the correctness of our stereochemical assignments, as the cis compounds are known, both from the data of others[13] and from metal–ammonia reduction of **4u** and **7u**, to be the more stable thermodynamically. The *trans*-methyl ketone **12t** fortunately became available by catalytic hydrogenation of **12u** and its stereochemistry was demonstrated by haloform cleavage to the trans acid.

Although we have not yet been able to synthesize the set in its entirety, we explored a number of reactions aimed at complete reduction of the angular function to a methyl group, including (1) $LiAlH_4$ treatment of **4u** tosylate and **4c** mesylate in ether, pyridine, THF, and DME under a variety of conditions; (2) LiH + $LiAlH_4$ treatment of **4u** tosylate and **4c** mesylate in THF;[14] (3) Li–NH_3 treatment of **4u** tosylate and **4c** mesylate;[15] (4) $LiAlH_4$ and $NaBH_4$ treatment of **5u** tosylhydrazone;[16] (5) PBr_3 treatment of **4u** in pyridine at 0 and 60°; (6) $(COCl)_2$ + pyridine treatment of **4u**.[17] The only reaction which gave angular group reduction without other disruptions of the molecule was Wolff–Kishner reduction[15,18] of the trans aldehyde **5t**. Curiously, the similar reduction of **5c** failed, as did the at-

(8) W. L. Garbrecht, *J. Org. Chem.*, **24**, 368 (1959).

(9) R. Adams and L. H. Ulich, *J. Amer. Chem. Soc.*, **42**, 599 (1920); A. L. Wilds and C. H. Shunk, *ibid.*, **70**, 2427 (1948); Ch. R. Engel and G. Just, *Can. J. Chem.*, **33**, 1515 (1955).

(10) J. A. Krynitsky and H. W. Carhart in "Organic Syntheses," Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, p 436.

(11) H. O. House and T. M. Bare in "Organic Syntheses," Vol. 49, K. B. Wiberg, Ed., Wiley, New York, N. Y., 1969, p 81; M. J. Jorgenson in "Organic Reactions," Vol. 18, W. G. Dauben, Ed., Wiley, New York, N. Y., 1970, p 1.

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(13) H. O. House and G. H. Ramusson, *J. Org. Chem.*, **28**, 31 (1963); and footnotes 8 and 9 in ref 3.

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(16) L. Caglioti and M. Magi, *Tetrahedron*, **19**, 1127 (1963); L. Caglioti, *ibid.*, **22**, 487 (1966).

(17) S. J. Rhoads and R. E. Michel, *J. Amer. Chem. Soc.*, **85**, 585 (1963).

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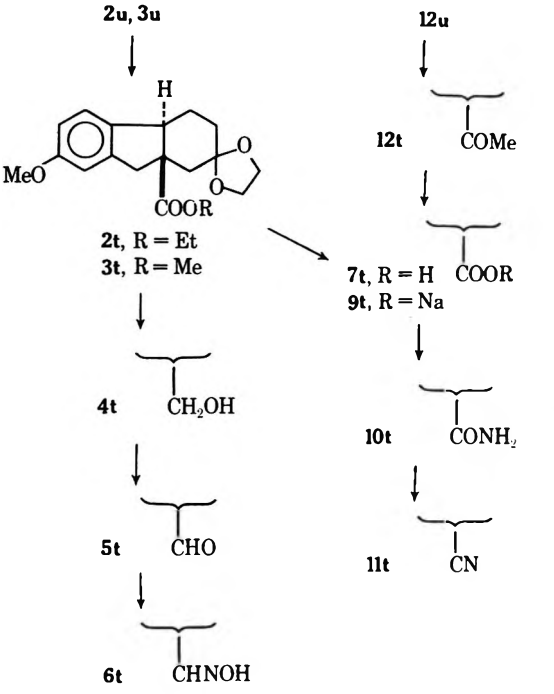
tempt with **5u** and with the mild Wolff–Kishner conditions (KO-*tert*-Bu + DMSO) introduced by Cram.[19] While we were able to isomerize the *trans*-methyl compound to cis by use of potassium amide, our attempts to utilize the former to make the unsaturated compound by benzylic bromination (NBS) led to introduction of bromine but apparently only at the benzylic methylene group, since we were unable to dehydrobrominate the product.

Because some amines are known to be catalyst poisons and hence interact strongly with catalyst surfaces, we particularly desired to obtain the aminomethyl set of compounds. Reduction of the three carboxamides (**10**) with $LiAlH_4$, using a variety of conditions and solvents, led to aminomethyl compound only from **10u** and then in disastrously low yield. The other compounds isolated in all cases were starting materials and carboxaldehydes (**5**), which arise from failure either of the intermediate iminate to undergo reduction or of the aluminoxyaminate precursor to form iminate by oxygen elimination. Further unsuccessful attempts to produce the aminomethyl compounds involved (1) $LiAlH_4$ treatment of the nitriles (**11**); (2) $LiAlH_4$ treatment of the aldoximes (**6**); (3) catalytic hydrogenation of the aldoximes (**6**) with Raney cobalt[20] at 40 atm and 65° and with 5% Rh/Al_2O_3[21] at 1 atm and 25°; (4) KNH_2 treatment of **4u** tosylate in refluxing ammonia, benzene and toluene; (5) NaN_3 treatment of **4u** tosylate and **4c** mesylate.[22]

In general our experience bore out the idea suggested by models that steric hindrance at the neopentyl carbon is greatest in the trans and least in the cis compounds. This is consistent with the behavior of the trans ester **2t** in the presence of DMSO anion; in the conversion of **7** into its acid chloride, reaction with the trans material would not proceed at the temperatures which sufficed for the unsaturated and cis compounds. In addition we observed that reactions involving attack at the neopentyl carbon invariably failed when that carbon was tetrahedrally hybridized. Although additions to a carbonyl group at this center did proceed in many instances, evidently the five coordination required for SN2 displacements at an already tetrahedral neopentyl carbon is excessively difficult in this crowded steric environment. Substitutions of the SN2 type at neopentyl carbons are normally very difficult but have been effected in some instances.[23] However, we are not aware of any reports of successful SN2 reactions at ring-juncture neopentyl carbons of this sort.[15] One attempt at such a displacement in this system, by acetylide on the tosylate of **4c**, has already been recorded.[4] Several more attempts were made in the present work with amide, azide, and borohydride, all with equal lack of success. Displacements with aluminohydride were in several instances apparently successful but led to loss of ketal and/or olefin as well.

SCHEME III
TRANS SERIES



Experimental Section[24]

CrO_3–Pyridine Preparation of Unsaturated Aldehyde 5u.—To a solution of unsaturated alcohol **4u** (879 mg, 3.05 mmol) in 15 ml of pyridine containing 1% water was added 43 ml of a saturated solution of CrO_3 in the same solvent. The flask, flushed with N_2 and stoppered, was allowed to stand at room temperature for 24 hr with stirring, after which 29 ml more of the CrO_3 solution was added and the mixture was stirred for an additional 48 hr under N_2. The reaction was worked up by addition of ether and filtration. The filtrate was passed through a short column of basic alumina, then concentrated and chromatographed, providing *ca.* 170 mg of tan solid, which was sublimed at 150° (0.01 mm) and recrystallized from pentane to give 160 mg (18%) of **5u** as light tan crystals: mp 154–156°; ir 2700, 1715, 1610, 1585, 935 cm^{-1} (ketal) with no absorption in the 3600–3200 cm^{-1} region; uv 218 nm (ϵ 11,900), 265 (12,900), 298 (5150); nmr δ 1.9 (1 H, d, J = 13 Hz), 2.55 (1 H d, J = 13 Hz), 2.5–2.9 (3 H complex), 3.2 (1 H, d, J = 16 Hz), 3.8 (3 H s), 3.95 (4 H m), 6.1 (1 H t, J = 4 Hz), 6.65–6.9 (2 H m), 7.35 (1 H d, J = 9.5 Hz), 9.75 (1 H s).

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.34; H, 6.37.

DCC–DMSO Preparation of 5u.—Solid dicyclohexylcarbodiimide (1.24 g, 6.0 mmol) was added to a solution of unsaturated alcohol **4u** (576 mg, 2.0 mmol) in 6 ml of dry 1:1 DMSO–benzene which contained dry pyridine (0.16 ml, 2.0 mmol) and trifluoroacetic acid (0.08 ml, 1.0 mmol). The flask was flushed with N_2 and stoppered and the suspension was stirred for 48 hr at room temperature, after which 25 ml of ether and a solution of anhydrous oxalic acid (540 mg, 6.0 mmol) in 5.0 ml of MeOH were added; gas was evolved and the suspension was stirred for 30 min. Water and ether were added and urea was removed by filtration. Separation and extraction of the filtrate provided an

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(20) W. Reeve and J. Christian, *ibid.*, **78**, 860 (1956).

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(22) A. K. Bose, J. F. Kistner, and L. Farber, *ibid.*, **27**, 2925 (1962).

(23) E. L. Eliel and F. H. Westheimer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, pp 76–79, 538–541; N. Kornblum and D. C. Iffland, *J. Amer. Chem. Soc.*, **77**, 6653 (1955); L. Friedman and H. Shechter, *J. Org. Chem.*, **25**, 877 (1960); G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Amer. Chem. Soc.*, **86**, 964 (1964).

(24) Melting points were determined with a Mel-Temp apparatus and are uncorrected; infrared (ir) spectra were taken, using a Beckman IR-10 or a Perkin-Elmer 457 spectrometer, on $CHCl_3$ solutions unless otherwise specified; ultraviolet (uv) spectra were determined with a Cary Model 14 spectrophotometer and employing 95% EtOH as solvent; nmr spectra were taken using a Varian A-60 or A-60A spectrometer and $CDCl_3$ solutions (CH_2Cl_2 and/or Me_4Si internal standard); mass spectra were obtained from a Perkin-Elmer Model 270 mass spectrometer; unless otherwise specified $MgSO_4$ was the drying agent and Florisil was the chromatograph absorbent employed; microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.; the abbreviations DCC, DME, DMSO, and THF refer to dicyclohexylcarbodiimide, dimethoxyethane, dimethyl sulfoxide, and tetrahydrofuran, respectively.

organic residue, chromatographed to give 400 mg (70%) of **5u**, crystallizing from pentane as a crude tan solid, mp 147–152°.

DCC–DMSO Preparation of Cis Aldehyde 5c.—By the procedure described in detail above for **5u**, cis alcohol **4c** (353 mg, 1.22 mmol) was oxidized over 24 hr. After work-up, the crude aldehyde was chromatographed and appropriate fractions were combined. Sublimation at 160° (0.01 mm) and recrystallization from pentane yielded 300 mg (85%) of **5c** as a white solid: mp 69–71.5° (lit.[4] mp 69.5–72°); ir (CCl_4) 2700, 1725, 1610, 935 cm^{-1}, no absorption in the 3600–3200 cm^{-1} region; nmr δ 1.25–2.3 (6 H complex), 2.75 (1 H d, J = 16 Hz), 3.05 (1 H d, J = 16 Hz), 3.55 (1 H t, J = 5 Hz), 3.8 (3 H s), 3.95 (4 H s), 6.65–6.9 (2 H m), 7.1 (1 H q, J = 1, 9.5 Hz), 9.85 (1 H s).

CrO_3–Pyridine Preparation of Trans Aldehyde 5t.—By the procedure described in detail above for **5u**, trans alcohol **4t** (430 mg, 1.48 mmol) was oxidized over 72 hr. The crude oxidation product was chromatographed and appropriate fractions were combined and crystallized, yielding 95 mg of yellow–brown solid, mp 124–126°, which was sublimed at 170° (0.01 mm) and recrystallized from hexane to give 90 mg (21%) of **5t** as white crystals: mp 128.5–130°; ir (CCl_4) 2740, 1720, 1615, 935 cm^{-1}, no OH absorption in the 3600–3200 cm^{-1} region; uv 227 nm (ε 6800), 285 (2930), 290 s (2520); nmr δ 1.6–3.2 (9 H complex), 3.8 (3 H s), 3.9 (4 H m), 6.6–6.85 (2 H m), 7.1 (1 H q, J = 1, 9 Hz), 9.65 (1 H s).

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.70; H, 7.00.

DCC–DMSO Preparation of 5t.—By the procedure described in detail above for **5u**, trans alcohol **4t** (500 mg, 1.73 mmol) was oxidized over 48 hr. The crude product was chromatographed and appropriate fractions were combined and crystallized from hexane to give 350 mg (71%) of **5t** as crude yellow crystals, mp 127–133°.

Unsaturated Aldoxime 6u.—By the general oximation procedure of Shriner, Fuson, and Curtin,[25] unsaturated aldehyde **5u** (500 mg, 1.75 mmol) was added to a suspension of $NH_2OH \cdot HCl$ (665 mg, 9.5 mmol) and NaOH (400 mg, 10 mmol) in 35 ml of absolute EtOH and refluxed for 18 hr under N_2. The mixture was concentrated under vacuum; the residue was taken up in 50 ml of water and acidified to pH 3–4 with saturated aqueous oxalic acid. Extraction with CH_2Cl_2 and concentration gave 474 mg of brown oily solid. Sublimation at 180° (0.01 mm) and recrystallizations from ether–CH_2Cl_2 provided 400 mg (76%) of **6u** as pale yellow needles: mp 172–174°; ir *ca.* 3350 (broad), 1610, 1585, 935 cm^{-1}, no C=O absorption; uv 261 nm (ε 15,300), 300 (4640); nmr δ 1.95 (1 H d, J = 13 Hz), 2.2–2.95 (4 H complex), 3.25 (1 H d, J = 16 Hz), 3.75 (3 H s), 3.95 (4 H s), 5.85 (1 H t, J = 4 Hz), 6.6–6.85 (2 H m), 7.25 (1 H d, J = 9 Hz), 7.55 (1 H s).

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36. Found: C, 67.61; H, 6.46.

Cis Aldoxime 6c.—By the procedure described in detail above for **6u**, cis aldehyde **5c** (320 mg, 1.11 mmol) was oximated over 8 hr to yield 330 mg of crude oily product, which was sublimed at 180° (0.01 mm) and crystallized from ether–pentane to yield 270 mg (80%) of **6c** as a white solid: mp 93–94°; ir *ca.* 3350 (broad), 1610, 1590, 930 cm^{-1}, no C=O absorption; uv 228 nm (ε 8180), 283 (2730), 288 s (2420); nmr δ 1.2–2.35 (6 H complex), 2.7 (1 H d, J = 16 Hz), 2.9–3.5 (2 H m), 3.75 (3 H s), 3.9 (4 H s), 6.6–7.15 (3 H m), 7.8 (1 H s).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98. Found: C, 67.23; H, 6.99.

Trans Aldoxime 6t.—By the procedure described in detail above for **6u**, trans aldehyde **5t** (350 mg, 1.22 mmol) was oximated over 18 hr to give 376 mg of crude solid. Sublimation at 180° (0.01 mm) and recrystallizations from CH_2Cl_2 yielded 225 mg (61%) of **6t** as white crystals: mp 195–197°; ir *ca.* 3350 (broad), 1615, 1590, 930 cm^{-1}, no C=O absorption; uv 228 nm (ε 8370), 282 (2760), 288 s (2450); nmr δ 1.0–3.0 (8 H complex) 3.1 (1 H d, J = 14.5 Hz), 3.75 (3 H s), 3.9 (4 H s), 6.5–7.1 (3 H complex), 7.5 (1 H s), 7.55 (1 H, broad).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98. Found: C, 67.20; H, 6.91.

Trans Carboxylic Acid 7t.—A solution of trans ethyl ester **2t** (1.8 g, 5.42 mmol) and KOH (4.0 g, 71 mmol) in 180 ml of 2-methoxyethanol was refluxed under N_2. After 24 hr the cooled mixture was acidified to pH 3–4 with saturated aqueous oxalic acid, then diluted with more water and extracted with CH_2Cl_2. Sublimation of the extraction residue at 150° (0.01 mm) and recrystallizations from absolute EtOH yielded 1.2 g (73%) of **7t** as white crystals: mp 198–200°; ir 3600–2300 (broad), 1715, 1610, 1585, 945 cm^{-1}; uv 219 nm (ε 7050), 228 (7210), 283 (2820), 290 s (2440); nmr δ 1.8 (1 H d, J = 13 Hz), 1.85–2.95 (7 H complex), 3.1 (1 H d, J = 15.5 Hz), 3.8 (3 H s), 3.9 (4 H m), 6.6–6.85 (2 H m), 7.05 (1 H d, J = 9 Hz), 10.6 (1 H s, broad).

Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.04; H, 6.60.

Identical material could be obtained in purified yields of *ca.* 75–80% by catalytic hydrogenation of **7u** under the conditions previously specified.[3]

Unsaturated Lithium Carboxylate 8u.—Unsaturated carboxylic acid **7u** (141 mg, 0.466 mmol) was added to a stirred suspension of LiH (3.4 mg, 0.425 mmol) in dry DME and the mixture was refluxed for 2 hr under N_2. The mixture was cooled in an ice–salt bath and the insoluble Li salt was removed by filtration. The solid was washed three times with 10-ml portions of hot benzene and then once with cold anhydrous ether; the solid was dried for 1 hr at room temperature under vacuum (1.0 mm) to give 111 mg (85%) of **8u** as an off-white solid displaying no C=O absorption in its ir spectrum (KBr).

Cis Lithium Carboxylate 8c.—By the procedure described above for **8u**, cis carboxylic acid **7c** (150 mg, 0.496 mmol) was converted to its lithium salt, which was purified to give 117 mg (76%) of **8c** as an off-white solid, whose ir spectrum (KBr) lacked C=O absorption.

Unsaturated Sodium Carboxylate 9u.—Unsaturated carboxylic acid **7u** (145 mg, 0.471 mmol) was added to a stirred suspension of 0.471 mmol of NaH (20.2 mg of 56% oil dispersion washed twice with pentane) in dry DME (25 ml) under N_2. The mixture was refluxed for 2 hr, then cooled and concentrated to dryness under vacuum. The solid residue was purified as described for the lithium salt to give 136 mg (93%) of **9u** as a light tan solid having no C=O absorption in its ir spectrum (KBr).

Trans Sodium Carboxylate 9t.—By the procedure described above for **9u**, trans carboxylic acid **7t** (150 mg, 0.496 mmol) was converted to its Na salt and the product was isolated and purified to give 110 mg (69%) of **9t** as an off-white solid whose ir spectrum (KBr) showed no C=O absorption.

Unsaturated Carboxamide 10u.—Unsaturated carboxylic acid **7u** (501 mg, 1.66 mmol) was added to a stirred solution of $LiOH \cdot H_2O$ (69.8 mg, 1.66 mmol) in 70 ml of MeOH and the solution was stirred overnight at room temperature and then concentrated to dryness under vacuum. The residual solid was taken up in 75 ml of dry benzene and the solution was reduced to $^1/_3$ volume by distillation at atmospheric pressure. To the stirred ice-cold benzene solution of the Li salt under N_2 was added dry pyridine (*ca.* 0.1 ml) and then oxalyl chloride (0.34 ml, 4.0 mmol). The resultant yellow suspension was allowed to warm to room temperature and then heated to 40–50° and stirred for 2 hr. Excess oxalyl chloride was removed under slight vacuum and the suspension of acid chloride was cooled to room temperature. The flask was then equipped with a Dry Ice condenser and anhydrous NH_3 (*ca.* 125 ml) was distilled into it. The suspension was stirred at reflux for 4 hr, the NH_3 was then allowed to evaporate, and the residue was extracted with water and CH_2Cl_2. Concentration of extracts gave 359 mg of crude yellow solid, which was chromatographed. Appropriate fractions were combined, sublimed at 170° (0.01 mm), and crystallized from 1:1 cyclohexane–benzene to give 260 mg (52%) of **10u** as white crystals: mp 161.5–163°; ir *ca.* 3530, *ca.* 3410, 1675, 1610, 1580, 940 cm^{-1}; uv 261 nm (ε 20,600), 300 (5930), 308 s (5170); nmr δ 1.7 (1 H d, J = 13 Hz), 2.6 (2 H t, J = *ca.* 3.5 Hz), 2.9 (1 H d, J = 16 Hz), 2.95 (1 H d, J = 13 Hz), 3.3 (1 H d, J = 16 Hz), 3.8 (3 H s), 4.0 (4 H s), 5.65 (2 H, broad), 6.0 (1 H t, J = 4 Hz), 6.65–6.9 (2 H m), 7.35 (1 H d, J = 9 Hz).

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36. Found: C, 67.89; H, 6.37.

Cis Carboxamide 10c.—By the procedure described in detail above for **10u**, cis carboxylic acid **7c** (518 mg, 1.71 mmol) was converted to the corresponding carboxamide, which was chromatographed. Appropriately combined fractions were purified by sublimation at 170° (0.01 mm) and recrystallizations from CH_2Cl_2 to give 400 mg (77%) of **10c** as white crystals: mp 178.5–179°; ir *ca.* 3480, *ca.* 3330, 1665, 1610, 1585, 925 cm^{-1}; uv 220 nm (ε 6740), 228 (7070), 282 (2680), 288 s (2390); nmr δ 1.3–2.3 (6 H complex), 2.8 (1 Hd, J = 16 Hz), 3.4–3.8 (2 H complex), 3.8 (3 H

(25) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964.

s), 3.95 (4 H m), *ca.* 5.8–7.3 (2 H, very broad), 6.65–6.9 (2 H m), 7.05 (1 H d, J = 9 Hz).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; mol wt, 303. Found: C, 67.13; H, 7.01; mol wt (mass spectrum), 303.

Trans Carboxamide 10t.—To a stirred suspension of LiH (8.0 mg, 1.0 mmol) in 40 ml of dry DME was added trans carboxylic acid **7t** (304 mg, 1.0 mmol) and the suspension was refluxed for 2 hr under N_2. The stirred mixture was cooled in an ice–salt bath and dry pyridine (*ca.* 0.1 ml) was added, followed by oxalyl chloride (0.60 ml, 7.0 mmol). The resultant yellow suspension was heated for 7 hr with stirring under N_2 at 45–55°; the mixture was then cooled; and excess oxalyl chloride was removed under slight vacuum.

The acid chloride (ir 1740, 1770 cm^{-1}) was treated with *ca.* 250 ml of anhydrous NH_3 for 6 hr as described for **10u**. Work-up provided 341 mg of crude oily product, which was chromatographed. Sublimation of appropriately combined fractions at 170° (0.01 mm) and recrystallizations from ether–$CHCl_3$ gave 55 mg (18%) of **10t** as fine white needles: mp 178–179.5°; ir 3500, 3400, 1665, 1610, 1580, 930 cm^{-1}; uv 220 nm (ϵ 6230), 228 (6670), 282 (2660), 288 s (2350); nmr δ 1.4–2.5 (6 H complex), 2.5–3.5 (3 H complex), 3.75 (3 H s), 3.95 (4 H s), 5.1 (2 H s, broad), 6.6–6.9 (2 H m), 7.05 (1 H d, J = 8 Hz).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; mol wt, 303. Found: C, 67.20; H, 7.01; mol wt (mass spectrum), 303.

Unsaturated Nitrile 11u.—To a stirred solution of unsaturated carboxamide **10u** (150 mg, 0.5 mmol) and dry pyridine (2.43 ml, 30 mmol) in 115 ml of dry THF under N_2 was added 0.55 ml (7.5 mmol) of $SOCl_2$ by syringe. The mixture was refluxed for 5 hr and cooled in an ice bath, and excess $SOCl_2$ was decomposed with aqueous NaOH. The extraction residue was chromatographed and appropriately combined fractions were sublimed at 175° (0.01 mm) and recrystallized from ether–$CHCl_3$ to give 91 mg (64%) of **11u** as white needles: mp 149.5–151°; ir (CCl_4) 2230, 1610, 940 cm^{-1}, no C=O absorption; uv 212 nm (ϵ 20,400), 261 (20,200), 298 (5650), 305 (5110); nmr δ 1.85 (1 H d, J = 13 Hz), 2.5 (1 H d, J = 13 Hz), 2.5–2.9 (2 H m), 2.9 (1 H d, J = 15.5 Hz), 3.4 (1 H d, J = 15.5 Hz), 3.8 (3 H s), 4.05 (4 H m), 5.95 (1 H t, J = 4 Hz), 6.65–7.0 (2 H m), 7.35 (1 H d, J = 9 Hz).

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05. Found: C, 71.83; H, 6.04.

Cis Nitrile 11c.—By the procedure described in detail above for **11u**, cis carboxamide **10c** (152 mg, 0.50 mmol) was dehydrated over 5 hr. The crude oily product was chromatographed and appropriate fractions were combined, recrystallized from pentane–ether, sublimed at 175° (0.01 mm), and recrystallized from ether to give 51 mg (36%) of **11c** as white shiny plates: mp 82–83°; ir (CCl_4) 2230, 1610, 935 cm^{-1}, no C=O absorption; uv 229 nm (ϵ 8420), 281 (2620), 288 s (2410); nmr δ 1.3–2.5 (6 H complex), 2.9 (1 H d, J = 15.5 Hz), 3.3 (1 H d, J = 15.5 Hz), 3.45 (1 H t, J = 4 Hz), 3.75 (3 H s), 3.95 (4 H m), 6.6–6.85 (2 H m), 7.0 (1 H d, J = 9 Hz).

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71. Found: C, 71.53; H, 6.69.

Trans Nitrile 11t.—By the procedure described above for **11u**, trans carboxamide **10t** (238 mg, 0.786 mmol) was dehydrated over 8 hr and the crude oily product was chromatographed. Appropriately combined fractions were sublimed at 180° (0.01 mm) and recrystallized from ether–$CHCl_3$ to give 126 mg (56%) of **11t** as white crystals: mp 144–145°; ir 2230, 1615, 1585, 950 cm^{-1}, no C=O absorption; uv 229 nm (ϵ 7840), 283 (2510), 289 s (2280); nmr δ 1.5–2.8 (7 H complex), 2.8 (1 H d, J = 15 Hz), 3.2 (1 H d, J = 15 Hz), 3.75 (3 H s), 4.0 (4 H m), 6.6–6.9 (2 H m), 7.1 (1 H d, J = 8 Hz).

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71. Found: C, 71.62; H, 6.70.

Unsaturated Methyl Ketone 12u.—Dry DMSO (3 ml) was added under N_2 to a flask containing 2.0 mmol of NaH (86 mg of 56% oil dispersion, washed twice with pentane) and the suspension was heated at 65–70° for 45 min with stirring until H_2 evolution ceased. The solution was cooled in an ice bath and 3 ml of dry THF was added, followed by unsaturated ester **2u** (330 mg, 1.0 mmol) in dry THF (3 ml). The green solution was stirred at room temperature for 2 hr under N_2; then excess DMSO anion was decomposed by careful addition of saturated aqueous Na_2SO_4 (1.0 ml) and the mixture was poured into 500 ml of water and acidified to *ca.* pH 4 with saturated aqueous oxalic acid. Extraction provided the β-keto sulfoxide as a brown viscous oil.

To a stirred solution of the crude β-keto sulfoxide in 1:10 water–THF (20 ml) was added Al·Hg prepared by dipping strips of Al foil (270 mg, 10 mg-atoms) into 2% aqueous $HgCl_2$ for *ca.* 1 min, then washing the strips in absolute EtOH, rinsing them in anhydrous ether, and cutting them into small rectangles directly into the reaction flask. The mixture was stirred at reflux for 2 hr under N_2, during which time gas was evolved, then cooled and filtered through Celite; the residue was washed thoroughly with 1:10 water–THF. The filtrate was concentrated to 5 ml, diluted with 50 ml of water, and extracted three times with ether; the extracts were combined and concentrated and the residual oil was passed in ether through a short column of Florisil. The eluate was concentrated and crystallized on standing; the crystalline material was sublimed at 170° (0.01 mm) and recrystallized from hexane–ether to give 110 mg (37%) of **12u** as white prisms: mp 123–125°; ir 1700, 1610, 1585, 1350, 935 cm^{-1}; uv 261 nm (ϵ 18,500), 301 (4140), 309 s (3660); nmr δ 1.75 (1 H d, J = 13 Hz), 2.0 (3 H s), 2.55 (2 H t, J = *ca.* 4 Hz), 2.8 (1 H d, J = 13 Hz), 3.0 (1 H d, J = 17 Hz), 3.1 (1 H d, J = 17 Hz), 3.75 (3 H s), 3.9 (4 H m), 5.95 (1 H t, J = 4 Hz), 6.65–6.9 (2 H m), 7.4 (1 H d, J = 9 Hz).

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.82; H, 6.73.

***cis*-Methyl Ketone 12c.**—By the procedure described in detail above for **12u**, *cis*-methyl ester **3c** (500 mg, 1.58 mmol) was converted to the β-keto sulfoxide, which was reductively cleaved with Al·Hg to give a crude oily product. This material was passed in 1:1 ether–CH_2Cl_2 through a short column of Florisil and the eluate was concentrated and crystallized from ether–pentane. The crystalline material was sublimed at 170° (0.01 mm) and recrystallized from ether–pentane to give 102 mg (21%) of **12c** as fine white needles: mp 114–116°; ir 1700, 1610, 1585, 1350, 925 cm^{-1}; uv 218 nm (ϵ 8340), 227 (6110), 282 (2780), 288 s (2450); nmr δ 1.15–2.35 (6 H complex), 2.2 (3 H s), 2.7 (1 H d, J = 15 Hz), 2.85 (1 H d, J = 15 Hz), 3.65 (1 H m), 3.75 (3 H s), 3.85 (4 H s), 6.6–6.85 (2 H m), 7.05 (1 H d, J = 9 Hz).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.71; H, 7.41.

***trans*-Methyl Ketone 12t.**—Unsaturated methyl ketone **12u** (173 mg, 0.563 mmol) was hydrogenated with stirring at room temperature and atmospheric pressure over 31.3 mg of 5% Pd/C catalyst in 9.2 ml of 2-methoxyethanol. After 2 hr the reaction mixture was filtered and concentrated under vacuum to give crystalline material which was recrystallized three times from anhydrous ether yielding 95.2 mg (56%) of **12t** as white needles: mp 130–131°; ir 1700, 1620, 1590, 950 cm^{-1}; uv 219 nm (ϵ 7300), 228 (7260), 283 (3020), 290 s (2570); nmr δ of 1.5–3.1 (9 H complex), 2.0 (3 H s), 3.7 (3 H s), 3.9 (4 H m), 6.55–6.85 (2 H m), 7.0 (1 H d, J = 9 Hz).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.72; H, 7.39.

Iodoform Cleavage[25] of *trans*-Methyl Ketone 12t.—*trans*-Methyl ketone **12t** (60.4 mg, 0.20 mmol) was dissolved in 10 ml of dioxane and heated to 60° under N_2. A 10% NaOH solution (1.0 ml) was added, followed by slow addition of a solution of 2.0 g of KI and 1.0 g of I_2 in 8.0 ml of water until a deep brown color persisted (*ca.* 2.1 ml required). Just enough 10% aqueous NaOH was then added to decolorize the solution and the mixture was heated at 80° for 8 hr under N_2. When the cooled solution was poured into 25 ml of water an immediate yellow precipitate formed and was removed by filtration and recrystallized from absolute EtOH to give 59 mg (75%) of CHI_3, mp 117–119° (lit.[25] mp 119–121°). The aqueous filtrate was acidified to pH 3–4 with saturated aqueous oxalic acid and extracted to give material which was crystallized from ether, providing 39 mg (64%) of **7t** as white shiny plates, mp 198–200°; all spectral data are identical with those of trans carboxylic acid **7t** and a mixture melting point with authentic **7t** was undepressed.

***trans*-9a-Methyl Compound.**—To a solution of trans carboxaldehyde **5t** (400 mg, 1.39 mmol) in 10 ml of triethylene glycol was added 85% hydrazine monohydrate (4.0 ml) and the mixture was heated at 110–115° for 1 hr under N_2. The condenser was then removed and 2.0 g (36 mmol) of KOH was cautiously added to the mixture, which was heated to 190° and the condenser and N_2 source were reconnected. The temperature was maintained at 190–200° for 2.5 hr, after which the cooled mixture was dissolved in 50 ml of water and the pH was adjusted to 8

with saturated aqueous oxalic acid. The aqueous solution was extracted to give 184 mg of crude oily product, which was passed in ether through a short column of Florisil. Sublimation at 65–70° (0.01 mm) and recrystallizations from pentane yielded 99 mg (26%) of white crystals: mp 54–55°; ir 1610, 1580, 1350, 925 cm^{-1}, no C=O absorption; uv 219 nm (ϵ 6960), 228 (7550), 282 (2720), 288 s (2360); nmr δ 0.85 (3 H s), 1.1–2.85 (9 H complex), 3.75 (3 H s), 3.9 (4 H m), 6.5–7.1 (3 H complex).

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.41; H, 8.16.

cis-9a-**Methyl Compound.**—Potassium amide was prepared by addition of 39 mg (1.0 mg-atom) of K to 15 ml of anhydrous NH_3 containing *ca.* 1 mg of $FeCl_3$ in a flask equipped with a Dry Ice condenser. The suspension was stirred for 30 min, during which time the color changed from blue to gray-black; to this was added a solution of 50 mg of *trans*-methyl compound (0.183 mmol) in 5 ml of dry THF. The mixture was refluxed for 4 hr and worked up by addition of excess solid NH_4Cl. The usual work-up provided 48 mg of crude oily product, which was chromatographed. Appropriately combined fractions were sublimed at 90° (0.01 mm) and recrystallized from pentane to give 25 mg (50%) of white needles; mp 93–94°; ir 1610, 1585, 1355 m, 925 cm^{-1}, no C=O absorption; uv 220 s nm (ϵ 7570), 228 (7850), 282 (2780), 228 s (2440); nmr δ 1.1–2.9 (9 H complex), 1.25 (3 H s), 3.7 (3 H s), 3.8 (4 H m), 6.45–6.65 (2 H m), 6.9 (1 H d, J = 8.5 Hz).

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.34; H, 8.17.

p-**Toluenesulfonate Ester of Unsaturated Alcohol 4u.**—To a cold solution of unsaturated alcohol **4u** (1.0 g, 3.47 mmol) in dry pyridine (10 ml) was added *p*-toluenesulfonyl chloride (820 mg, 4.31 mmol) and the flask was flushed with N_2 and stoppered; the mixture was stirred for 4–5 hr at 0° and then at room temperature for 24 hr. The mixture was recooled to 0° and neutralized with dilute aqueous HCl. Extraction of the diluted mixture provided material which was crystallized from ether to give 563 mg (37%) of tan solid, mp 109–112°, ir 1350 cm^{-1}, no OH absorption in the 3600–3200 cm^{-1} region.

The *p*-**toluenesulfonate ester of cis alcohol 4c** and its preparation have been described previously.[4]

Methanesulfonate Ester of Cis Alcohol 4c.—To a stirred, ice-cold solution of cis alcohol **4c** (1.5 g, 5.28 mmol) in dry pyridine (10 ml) was added freshly distilled methanesulfonyl chloride (0.63 ml, 7.0 mmol) and the flask was flushed with N_2 and stoppered; the solution was stirred for 4–5 hr in an ice bath at 0° and then at room temperature for 32 hr. The mixture was recooled to 0° and neutralized with dilute aqueous HCl. Extraction of the diluted solution gave a viscous yellow oil, which failed to crystallize from a variety of solvents: ir 1370, 1350 cm^{-1}, no OH absorption in the 3600–3200 cm^{-1} region.

Registry No.—**4c** (methanesulfonate), 33885-17-5; **4u** (tosylate), 33885-18-6; **5c**, 13673-64-8; **5t**, 33885-20-0; **5u**, 33885-21-1; **6c**, 33885-22-2; **6t**, 33885-23-3; **6u**, 33885-24-4; **7t**, 33872-69-4; *cis*-9a-methyl compound, 33885-25-5; *trans*-9a-methyl compound, 33885-26-6; **10c**, 33885-27-7; **10t**, 33885-25-8; **10u**, 33885-29-9; **11c**, 33885-30-2; **11t**, 33885-31-3; **11u**, 33885-32-4; **12c**, 33885-33-5; **12t**, 33885-34-6; **12u**, 33885-35-7.

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The Resolution and Absolute Configuration of 7-Methylhexahelicene

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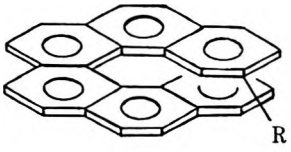
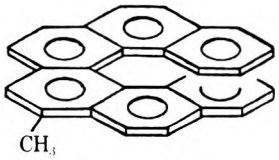
rac-7-Methylhexahelicene (**3**) is brominated to the bromomethyl derivative **4** which on treatment with trimethylphosphine is converted into the racemic quaternary phosphonium bromide **5**. By salt formation with silver D(−)-hydrogendibenzoyltartrate and recrystallization of same, a pure diastereoisomeric salt (−)-**6**$^+$·D(−)-HDBT$^-$ is isolated and converted into (−)-**5** by treatment with tetraethylammonium bromide. Aqueous alkaline treatment of (−)-**6**$^+$·D(−)-HDBT$^-$ affords (−)-**3**. All steps proceed in high yield. The above reactions provide a new method of resolution for methyl derivatives of dissymetric aromatic hydrocarbons.

When the work herein reported was started the absolute configuration of hexahelicene (**1**)[2] had not been



1, R = H

2, R = Br



(−)-3

established. Recently, the assignment of the left-handed helix (−)-**1**, as shown in the formula, has been established by X-ray analysis of (−)-2-bromohexahelicene (**2**).[3]

Because of the difficulty experienced in resolution of hexahelicene[2,4] by the use of α-(2,4,5,7-tetranitro-9-fluorenylidenaminooxy)propionic acid (TAPA),[5] a new method for the resolution of a helicene was sought which would involve a compound whose absolute configuration could be established by X-ray crystallographic methods. This method has been discovered and is described herein. However, since the problem of the helicenes has been solved[3] the X-ray work has not been carried out. Our method is outlined in Chart I.[6]

Bromination of 7-methylhexahelicene (**3**)[7] to 7-

(1) Postdoctoral fellow supported by Grant G12445X of the National Science Foundation.

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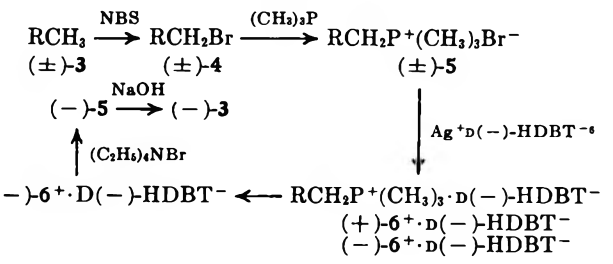
(4) M. S. Newman, R. S. Darlak, and L. Tsai, *J. Amer. Chem. Soc.*, **89**, 6191 (1967).

(5) M. S. Newman and W. B. Lutz, *ibid.*, **78**, 2469 (1956).

(6) Ag$^+$D(−)-HDBT$^-$ is silver D(−)-hydrogendibenzoyltartrate, a compound first used for resolution of an asymmetric tetracovalent phosphorus compound by D. M. Coyne, W. E. McEwen, and C. A. VanderWerf, *J. Amer. Chem. Soc.*, **78**, 3061 (1956). Both the D(−)- and L(+)-dibenzoyltartaric acids can be obtained from the Norse Laboratories, Inc., Santa Barbara, Calif. 93103.

(7) 7-Methylhexahelicene was first prepared here (unpublished work) by Dr. David J. Collins in 1959.

CHART I



hexahelicylmethyl bromide (**4**)[8] was accomplished in good yield with *N*-bromosuccinimide. Treatment of **4** with trimethylphosphine afforded the beautifully crystalline phosphonium salt **5** in almost quantitative yield. On reaction of **5** with silver D(−)-hydrogendibenzoyltartrate in methanol a high yield of a mixture of diastereoisomeric D(−)-HDBT salts (**6**) was obtained. On one crystallization from ethanol–1-propanol about 50% of the theoretical amount of the (−)$6^+\cdot$D(−)-HDBT$^-$ isomer separated. Further recrystallization did not appreciably improve the specific rotation. On refluxing (−)-$6^+\cdot$D(−)-HDBT$^-$ in methanol with tetraethylammonium bromide conversion to (−)-**5** was obtained in over 90% yield. This salt was readily crystallized from methanol–ether to yield crystals which seemed suitable for X-ray studies. Finally, on treatment of (−)-**5** with aqueous sodium hydroxide at room temperature (−)-**3** was obtained in high yield.[9] We assume that (−)-**3** and (−)-**5** exist as left-handed helices, as established for (−)-**1**, because of the similarity of the negative Cotton effect observed in the regions examined.[3]

This method of resolution is of special interest because a quaternary phosphonium compound **5**, in which the dissymmetry is not centered on phosphorus, has successfully been resolved. In addition, the ease of crystallization and separation of the diastereoisomeric phosphonium salts makes the resolution relatively simple.

Experimental Section[10]

(±)-**7-Methylhexahelicene** (**3**).[7]—A Grignard reagent was prepared by treating 1.67 g of magnesium in 50 ml of ether with 9.8 g of methyl iodide. After all of the magnesium had reacted, 300 ml of benzene was added and the ether was largely removed by distillation. To this reagent was added a solution of 20 g of 7,8,8a,9,10,16c-hexahydro-7-oxohexahelicene[4] in 500 ml of benzene. After being refluxed for 26 hr the mixture was worked up as usual. Chromatography over silica gel in benzene yielded 14.0 g of a first fraction from which a light yellow solid, presumably the expected olefin, mp 192–197°, could be crystallized. In addition, a second fraction from which 2.0 g of starting ketone could be crystallized and 1.4 g of a third fraction, presumably the tertiary alcohol, were obtained. The crude olefin (9.2 g) was aromatized as described[4] for the preparation of hexahelicene to yield 3.87 g (42%) of (±)-**3**, mp 192–194°. By chromatography and recrystallization from benzene–Skellysolve F, acetone, and benzene there was obtained the analytical sample, mp 198.0–198.5°. For further work, material of mp 192–194° was used.

Anal. Calcd for $C_{27}H_{18}$: C, 94.6; H, 5.2. Found: C, 94.7; H, 5.3.

(±)-**7-Hexahelicylmethyl Bromide** (**4**).[8]—A solution of 0.613 g of *N*-bromosuccinimide and 1.00 g of **3** in 10 ml of carbon tetrachloride was refluxed for 12 hr after the addition of a few crystals of benzoyl peroxide. On cooling the succinimide was removed by filtration and the filtrate was evaporated to dryness. Recrystallization of the residue from benzene–Skellysolve B yielded 0.99 g (78%) of **4**, mp 207–210°, suitable for further work. The analytical sample, mp 213–215°, was obtained by further recrystallization from the same solvent.

Anal. Calcd for $C_{27}H_{17}Br$: C, 77.1; H, 4.1; Br, 19.0. Found: C, 77.2; H, 4.2; Br, 19.1.

In a larger run (2.38 g of **3**) the yield of **4** was 70%.

(±)-**7-Hexahelicylmethyltrimethylphosphonium Bromide** (**5**).—To a solution of 1.00 g of **4** in 20 ml of ether and 20 ml of benzene in a three-necked flask under nitrogen equipped with a Dry Ice cooled condenser, septa, and magnetic stirrer was added about 1.5 ml of Dry Ice cooled trimethylphosphine (caution, toxicity) from a syringe. Solid **5** precipitated immediately. The mixture was stirred overnight (with water condenser instead of Dry Ice condenser) and then heated to reflux for 4 hr. The yellow solid was collected by filtration and the cooled mixture was washed with dry benzene. After drying *in vacuo* the solid was dissolved in 100 ml of hot methanol and the solution was concentrated to *ca.* 30 ml. On cooling 1.105 g (93%) of **5**, mp *ca.* 350° dec after darkening at 335°, nmr [CD_3OD–(CD_3)$_2$SO, 1:1] δ (TMS) 2.0 [9 H, d, J = 14.5 Hz, P(CH_3)$_3$], 4.59 (2 H, d, J = 17.5 Hz, –CH_2P), 6.3–8.8 (15 H, m, ArH), was obtained suitable for further use.

Anal. Calcd for $C_{30}H_{26}BrP$: C, 72.4; H, 5.2; Br, 16.1; P, 6.2. Found: C, 72.3; H, 5.3; Br, 15.9; P, 6.0.

The phosphonium bromide **5** slowly absorbs moisture on standing. As a result, marked solubility differences were observed during the recrystallization process. The presence of moisture, as revealed by the strong O–H stretching absorption in the ir spectrum, was gradually removed by heating.

(−)-**7-Hexahelicylmethyltrimethylphosphonium** D(−)-**Hydrogendibenzoyltartrate** [(−)-$6^+\cdot$D(−)-**HDBT**$^-$)].—To a solution at room temperature (previously warmed to effect solution) of 1.004 g of **5** in 50 ml of methanol was added 0.951 g of silver D(−)-hydrogendibenzoyltartrate prepared[6] from D(−)-dibenzoyltartaric acid, $[\alpha]^{27}D$ −111°. The heterogeneous mixture was magnetically stirred at ambient temperature for 17 hr in the dark. After addition of 15 ml of methanol the yellow suspension was heated to reflux for 72 hr. The silver bromide (89%) was collected by filtration and washed well with methanol. The filtrate was evaporated to dryness and the residue was stirred for 1 hr with 125 ml of distilled water. The solid was collected, washed with water, and dried *in vacuo* over P_2O_5 to yield 1.353 g (87%) of (±)-$6^+\cdot$D(−)-HDBT$^-$: mp 158–159° dec; ir 3500 (OH), 1730 cm^{-1} (s) (C=O); nmr (CD_3OD) δ (TMS) 1.85 [9 H, d, J = 14.5 Hz, P(CH_3)$_3$], 4.37 (2 H, d, J = 16 Hz, –CH_2P), 6.05 (2 H, s, methine H of HDBT), 6.3–8.4 [25 H, m, (Ar H, C_6H_5)]. The acidic proton was not observed because of exchange with the deuterated solvent. Recrystallization of the crude salt from 70 ml of ethanol–1-propanol (1:1) yielded 402 mg of (−)-$6^+\cdot$D(−)-HDBT$^-$ as yellow crystals, mp 157.5–158.5° dec, after 12 hr. The specific rotations were obtained at the wavelengths indicated[10] from 0.574 mg of salt in 2 ml of absolute methanol: −1105° (589 mμ), −1181° (578), −1457° (546), −4231° (436), and 0° (365). After two further recrystallizations from ethanol, 136 mg of (−)-$6^+\cdot$D(−)-HDBT$^-$ was obtained which gave the following specific rotations from a solution of 0.128 mg in 2 ml of methanol: −1109° (589), −1297° (578), −1625° (546), −4672° (436), and 0° (365). Hence we believe that almost completely resolved material was obtained in the first crystallization. The crystals from the first crop evidently retained one molecule each of ethanol and 1-propanol as

(8) The bromination of **3** was done here by Dr. R. A. Darlak in 1965.

(9) For analogous reactions, see A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, New York, N. Y., 1967, p 254.

(10) Melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus. A melting point block was used for those above 280°. Infrared were obtained on a Perkin-Elmer Infracord Model 137 spectrophotometer in KBr pellets. Nuclear magnetic resonance spectra were determined on a Varian 60 high-resolution spectrometer using TMS as an internal standard. The mass spectra were determined by use of the direct inlet system on an AEI MS-902 double-focusing mass spectrometer. Optical rotations were measured on a Perkin-Elmer Model 141 Polarimeter (accurate to 0.001°) using a 10-cm Micro-cell with inner glass tube diameter of 3.4 mm and a cell volume of 1 ml. In a typical rotation determination, the sample was weighed on a Cahn Electro-Balance (accurate to 0.001 mg), dissolved in a suitable solvent in a 2-ml Kimax volumetric flask, and 1 ml of the prepared solution of known concentration was transferred into the Micro-cell for immediate measuring in the instrument. Measuring accuracy with micro cells is claimed to be approximately ±0.2% for rotations >1° by the manufacturer. Elemental microanalyses were determined by Galbraith Laboratories, Knoxville, Tenn.

judged by the analysis. Such inclusion of solvent is not uncommon with phosphonium salts.[11]

Anal. Calcd for $C_{44}H_{39}O_5P \cdot C_2H_6O \cdot C_3H_8O$: C, 72.5; H, 6.0; P, 3.5. Found: C, 72.5; H, 5.7; P, 3.4.

(−)-7-Hexahelicylmethyltrimethylphosphonium Bromide (5).—A solution of 120 mg of (−)-6$^+$·D(−)-HDBT$^-$ ([α]^{23}D −1109°) and 3.5 g of tetraethylammonium bromide in 18 ml of methanol was refluxed for 48 hr and allowed to stir at room temperature for 72 hr. The methanol was removed under reduced pressure and the residue was stirred with 40 ml of water for 12 hr. The solid was collected by filtration, washed with water, and dried *in vacuo* over P_2O_5. Crystallization from methanol afforded 72.9 mg (95%) of (−)-5, mp *ca.* 354° dec. The infrared spectrum was identical with that of (±)-5. The following specific rotations were obtained at 23° from a solution of 0.400 mg in 2 ml of methanol: −1930° (589 mμ), −2070° (578), −2559° (546), −7563° (436), and 0° (365). Further recrystallization from methanol did not change the rotation significantly.

(−)-7-Methylhexahelicene (3).—A solution of 20 mg of (−)-5 ([α]^{23}D −1881°) was stirred with 5 ml of 10% sodium hydroxide at ambient temperature for 24 hr. The yellow solid was collected by filtration and washed well with water. After drying *in vacuo* over P_2O_5, there was obtained 12.6 mg (92%) of (−)-3, mp 175–180°. One recrystallization from 2-propanol yielded 10.5 mg of (−)-3, mp 185–186°, with the following specific rotations (from 0.356 mg in 2 ml of chloroform): −3157° (589 mμ), −3399° (578), −4185° (546), −12,332° (436), and +219° (365). The structure of (−)-3 was established by comparison with that of (±)-3 with respect to ir and mass spectrum (M$^+$, 342).

Registry No.—(±)-3, 33835-50-6; (−)-3, 33835-51-7; (±)-4, 33872-33-2; (±)-5, 33835-52-8; (−)-5, 33835-53-9; (±)-6$^+$·D(−)-HDBT$^-$, 33835-54-0; (−)-6$^+$·D(−)-HDBT$^-$, 33835-55-1.

(11) M. Davis and F. G. Mann, *J. Chem. Soc.*, 3770 (1964); C. H. Chen and K. D. Berlin, *J. Org. Chem.*, **36**, 2791 (1971).

The Conformations of Electronegatively Substituted Imines

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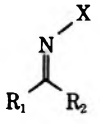
The preferred conformations of 1,1,1-trifluoroacetone hydrazone and azine have the substituent anti to the trifluoromethyl group. The assignments are based on the stereospecificity of six-bond, proton–fluorine coupling in selected *N,N*-dimethyl derivatives and correlations of the fluorine chemical shifts of syn and anti trifluoromethyl groups in hexafluoroacetone imine derivatives. Allylic proton–fluorine coupling is not a reliable indicator of stereochemistry.

The preferred conformations of unsymmetrical imines, hydrazones, oximes, azines, etc., are of continuing interest.[1] A related problem in symmetrical derivatives is the correct spectral identification of the syn and anti groups.[2] For those classes of compounds 1 where R_1 and R_2 are hydrocarbon, steric arguments suffice to predict conformation.[1,3,4]

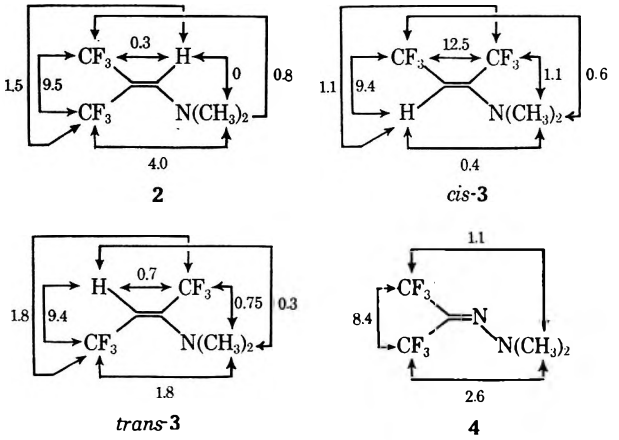


1, X = H, CH_3, NH_2, OH, F...
1a, $R_1 = CF_3$, $R_2 = CH_3$, X = NH_2

Trifluoroacetone hydrazone[5] (1a) and trifluoroacetone azine have single conformations in solution. Although steric arguments predict that the trifluoromethyl and the substituent should be anti,[6] dipole interactions between electronegative substituents may stabilize the syn form.[7] The purpose of this study is to determine the conformation of trifluoroacetone imine derivatives.

Results.—No single, simple, physical measurement unambiguously identifies the conformations of trifluoroacetone imines. Therefore a series of indirect studies was performed.

Six-Bond, Proton–Fluorine Coupling.—The methyl protons of enamine 2[8] couple differently to the cis and



2 *cis*-3 *trans*-3 4

trans trifluoromethyl groups. A 1.8-Hz, six-bond, proton–fluorine coupling was observed in the *trans*-hexafluorobutyne–dimethylamine adduct **3**, but the coupling in the cis isomer was not mentioned.[9] Couplings between all pairs of nuclei in both *cis*- and *trans*-3 have now been observed and include the 0.6-Hz, six-bond, proton–fluorine coupling in *cis*-3. Hexa-

(1) G. J. Karabatsos, J. D. Graham, and F. M. Vane, *J. Amer. Chem. Soc.*, **84**, 753 (1962); G. J. Karabatsos, F. M. Vane, R. A. Taller, and N. Hsi, *ibid.*, **86**, 3351 (1964).

(2) For the use of the new Eu chelates to identify oxime conformations see Z. W. Wolkowski, *Tetrahedron Lett.*, 825 (1971); K. D. Berlin and S. Rengaraju, *J. Org. Chem.*, **36**, 2912 (1971).

(3) E. Arnal, J. Elguero, R. Jacquier, C. Marzin, and J. Wylde, *Bull. Chem. Soc. Fr.*, 877 (1965); J. Elguero, R. Jacquier, and C. Marzin, *ibid.*, 713 (1968).

(4) Yu. P. Kitaev, B. I. Buzykin, and T. V. Troepol'skaya, *Russ. Chem. Rev.*, 441 (1970).

(5) R. A. Sheppard and P. L. Sciaraffa, *J. Org. Chem.*, **31**, 964 (1966).

(6) R. Filler in "Advances in Fluorine Chemistry," Vol. 6, J. C. Tatlow, R. D. Peacock, and H. H. Hyman, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1970.

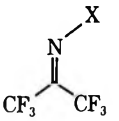
(7) H. G. Viehe, *Chem. Ber.*, **93**, 1697 (1960); R. E. Wood and D. P. Stevenson, *J. Amer. Chem. Soc.*, **63**, 1650 (1941).

(8) Yu. A. Cheburkov, N. Mukhamadaliev, Yu. E. Aronov, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1478 (1965).

(9) W. R. Cullen, D. S. Dawson, and G. E. Styan, *Can. J. Chem.*, **43**, 3392 (1965).

fluoroacetone dimethylhydrazone (**4**) shows similar stereospecific, six-bond, proton–fluorine coupling. The two compounds **3** are distinguished by the well-established stereospecific, five-bond, fluorine–fluorine coupling.[10] The trifluoromethyl assignments for **2** and **4** follow from the six-bond, proton–fluorine coupling and the fluorine chemical shifts which are discussed below. No six-bond, proton–fluorine coupling is visible in trifluoroacetone dimethylhydrazone.

Chemical Shifts of Hexafluoroacetone Derivatives.— Syn and anti trifluoromethyl groups of some HFA derivatives have been assigned by long-range coupling considerations. The surest of these is the *N*-fluoroimine **5a**, for which the upfield, anti trifluoromethyl



5a, X = F **d**, X = $N(CH_3)_2$
b, X = H **e**, X = NH_2
c, X = CH_3

group has a fluorine–fluorine coupling half that of the downfield syn group.[11] Similar arguments based on proton–fluorine coupling led to identical assignments for the imine **5b**,[12] the *N*-methylimine **5c**,[12] and now for the *N*,*N*-dimethylhydrazone **5d**. Similar assignments can probably be made for other HFA imine derivatives and are summarized in Table I.

TABLE I
FLUORINE NMR PARAMETERS OF HEXAFLUOROACETONE IMINE DERIVATIVES

X	Chemical shift (anti) (*J*, Hz)	Chemical shift (syn) (*J*, Hz)	Ref
H	−75.4 (0)	−73.6 (2.5)	*a*
CH_3	−71.3 (1.8)	−65.2 (2.5)	
NH_2	−66.7	−64.9	
OH	−67.7	−65.6	*a*
F	−66.8 (12)	−63.6 (24)	*b*
Cl	−69.1	−67.5	*b*
Br	−70.9	−69.9	*a*
$N(CH_3)_2$	−63.8 (1.1)	−52.1 (2.6)	
OCH_3	−67.3	−65.1	
	−68.6	−65.1	*c*
	−68.7	−65.0	*c*
HFA	−84.6		*d*

[a] Reference 12. [b] Reference 11. [c] Reference 14. [d] C. H. Dungan and J. R. Van Wazer, "Compilation of Reported F^{19} NMR Chemical Shifts," Wiley-Interscience, New York, N. Y., 1970.

While changes in the chemical shifts of the anti trifluoromethyl groups are small, the syn trifluoromethyl in dimethylhydrazone **5d** is shifted downfield 13 ppm from that in hydrazone **5e**. The cis trifluoromethyl group in enamine **2** is also shifted downfield. The chemical shifts of the trifluoromethyl groups of trifluoroacetone derivatives, including the *N*,*N*-dimethylhydrazone, are relatively insensitive to imine substitution. Thus trifluoroacetone hydrazone is assigned the conformation with the amino group anti to the trifluoromethyl group. See Table II.

TABLE II
FLUORINE CHEMICAL SHIFTS OF TRIFLUOROACETONE IMINE DERIVATIVES

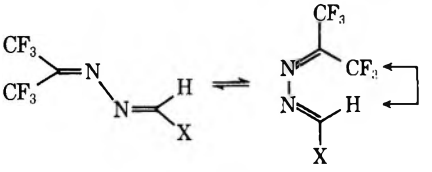
X	Chemical shift, ppm
NH_2	−71.4
OH	−72.1
$N(CH_3)_2$	−72.1
	−73.5
TFA[a]	−82.6

[a] C. H. Dungan and J. R. Van Wazer, "Compilation of Reported F^{19} NMR Chemical Shifts," Wiley-Interscience, New York, N. Y., 1970.

Discussion

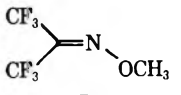
Burton[13] observed that cis four-bond, proton–fluorine coupling in the hydrogen chloride adducts of hexafluorobutyne was larger than trans coupling. This correlation has been used to assign the configuration of some HFA imines (correctly),[12] but in **2** and **3** the trans four-bond, proton–fluorine coupling is larger than the cis. Caution should be used in applying four-bond coupling as a criterion of stereochemistry. Signs of these couplings are unknown.

Both the benzaldehyde **6a** and isobutyraldehyde **6b**



6a, X = C_6H_5
b, X = $CH(CH_3)_2$

azines of HFA show stereospecific, six-bond, proton–fluorine coupling between the aldehyde proton and the syn trifluoromethyl group.[14] What part through space interactions in cisoid conformations play in determining the stereospecificity of the couplings is unknown. Unless both cis and trans couplings are available, such as with **3** or HFA derivatives, the structure should not be based on six-bond coupling. Six-bond couplings in hexafluoroacetone oxime *O*-methyl ether (**7**)[12] and in the methanol adduct with hexafluorobutyne **8**[15] are not observable.



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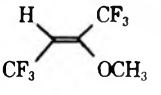

8

Experimental Section

Proton nmr spectra were determined on a Varian A-60 and fluorine nmr spectra on a Varian A56/60. The preparation of **1a** has been described previously.[5] The mixture **3** was prepared by bubbling dimethylamine through a trichlorofluoromethane solution of hexafluorobutyne until no further exotherm was observed.[9] Examination of the crude product verified the presence of both isomers; distillation gave only the trans isomer.

(10) G. V. D. Tiers, *J. Chem. Phys.*, **35**, 2263 (1961).
(11) J. K. Ruff, *J. Org. Chem.*, **32**, 1675 (1967).
(12) W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **30**, 1398 (1965).
(13) D. J. Burton, R. L. Johnson, and R. T. Bogan, *Can. J. Chem.*, **44**, 635 (1966).
(14) F. J. Weigert, submitted for publication in *J. Fluorine Chem.*
(15) E. K. Raunio and T. G. Frey, *J. Org. Chem.*, **36**, 345 (1971).

Several weeks at room temperature were required for the re-equilibration.

Hexafluoroacetone Dimethylhydrazone (4).—2,2,2-Trifluoro-1-(trifluoromethyl)ethylidenimine (11 ml) was bubbled into a chilled solution of 6.0 g of *N*,*N*-dimethylhydrazine in 25 ml of ether. After the addition was complete, the solution was warmed to room temperature and poured onto 30 g of phosphorus pentoxide.

Distillation gave only a trace of the desired hydrazone. The product was purified by gas chromatography on a 6 ft × 0.25 in. column of 20% silicone #200 on 60/80 Chromo "W." At 50° and 10 cc/min the retention time was 50 min; pmr (CCl_4) δ 3.24 (q, J = 1.2, q, J = 2.4 Hz).

Anal. Calcd for $C_5H_6F_6N_2$: mol wt, 208.0434. Found: mol wt, 208.0429 (high-resolution mass spectrum).

1-[1-(Trifluoromethyl)ethylidenehydrazono]-1-(trifluoromethyl)ethane.—To a stirred solution of 25 g of trifluoroacetone in 200 ml of ether at −30° was added dropwise 25 g of anhydrous hydrazine. An extremely exothermic reaction occurred. The solution was allowed to warm to room temperature and phosphorus pentoxide was added until further addition produced no change. The solution was distilled through a spinning-band column, giving 10 g of product as a pale yellow liquid: bp 58–62° (180 mm); ^{19}F nmr (CCl_4) δ −73.48 (s); pmr δ 1.5 (s); ir (CCl_4) 7.5, 8.3, 8.7, and 9.0 μ.

Anal. Calcd for $C_6H_6F_6N_2$: C, 32.8; H, 2.8. Found: C, 32.8; H, 3.0.

Trifluoroacetone Dimethylhydrazone.—To a solution of 11.2 g of trifluoroacetone in 25 ml of ether at −20° was added dropwise with stirring under nitrogen 6 g of *N*,*N*-dimethylhydrazine. The solution was stirred for 1 hr at room temperature after the addition was complete. Phosphorus pentoxide was added until no further exotherm was observed. The liquid was distilled through a small spinning-band column, giving 2.5 g of product as a colorless liquid: bp 100–103°; ir (CCl_4) 3.3, 3.45, 6.8, 6.9, 7.4, 8.3, 9.0, 9.8, 10.4, and 14.4 μ; pmr δ 2.00 (s, CCH_3), 2.67 (s, NCH_3).

Anal. Calcd for $C_5H_9F_3N_2$: mol wt, 154.0718. Found: mol wt, 154.0717 (high-resolution mass spectrum).

Registry No.—**1a** (X = NH_2), 34226-09-0; **1a** (X = OH), 34226-10-3; **1a** [X = $N(CH_3)_2$], 34226-11-4; **1a** [X = $N{=}C(CH_3)CF_3$], 34226-12-5; *cis*-**3**, 4639-94-5; *trans*-**3**, 4592-87-4; **4**, 34224-15-2.

7,8,9-Trimethoxy-4a,10b-*trans*- and -4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridines. Configurational and Conformational Changes in Epimerization of N-Substituted Derivatives[1]

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Proton exchange and epimerization of salts of N-substituted 7,8,9-trimethoxy-4a,10b-*trans*- and -4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridines were studied by nmr. The hydrochloride salts of the *N*-methyl derivatives of the trans and cis isomers each crystallize to give only one epimeric form, **5a** and **6a**, respectively. In formic acid proton exchange and equilibration of epimers are relatively slow processes and the equilibration is catalyzed by sodium formate. Crystalline **5a** dissolved in formic acid is shown to have the cyclohexane and hetero rings in chair and half-chair conformations, respectively, with the *N*-methyl group in equatorial orientation and cis to H-4a. Epimerization of **5a** involves an inversion of the nitrogen without any change in conformations of the six-membered rings. The nmr data for the crystalline cis isomer **6a**, in formic acid, indicates chair and half-chair conformations of the two rings, with H-4a having an equatorial orientation relative to the cyclohexane ring and being axial relative to the hetero ring, with the *N*-methyl group equatorial and cis to H-4a. Epimerization to **6b** is associated with an inversion of conformation of the hetero and cyclohexane rings; thus the *N*-methyl group has an equatorial orientation in both epimers. Exchange processes were also investigated to a limited extent in other solvents, including chloroform-*d*, trifluoroacetic acid, and D_2O. The conformations of the free bases are also discussed.

7,8,9-Trimethoxy-4a,10b-*trans*- and -4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridines and a number of N-substituted derivatives have been prepared by known methods from *trans*- and *cis*-2-(3,4,5-trimethoxyphenyl)cyclohexylamines[2] (**1** and **2**) for pharmacological evaluation.

Under conditions of slow proton exchange on the nmr time scale, the nmr spectra of the salts of the tertiary amines showed an equilibration between two geometrical isomers. This epimerization was studied more extensively in the hydrochloride salts of the *N*-methyl isomers **5** and **6**. The hydrochloride salts of **5** and **6** each crystallize in a single epimeric form, the form that is thermodynamically most stable in solution in each case. The nmr spectra of freshly prepared solutions of the crystalline salts of **5** or **6** dissolved in formic acid show the presence of only one epimer in each case (**5a** or **6a**), followed by a slow appearance of a second minor isomer (**5b** or **6b**). The rate of equilibration is enhanced by sodium formate. Melts of the salts give the spectra of the equilibrated systems.

Spectrum A, Figure 1, shows part of the nmr spectrum of a solution of the crystalline hydrochloride salt of **5** in 99% formic acid, and spectrum B is that of the equilibrated system after addition of sodium formate. Spectrum A indicates the presence of a single epimer. The most relevant signals are the *N*-methyl doublet at τ 6.83 (J_{NH-CH_3} = 5 Hz) and the signals of the diastereotopic hydrogens on C-6 which appear as sets of doublets of doublet with chemical shifts of τ 5.29 and 5.68. The C-6 hydrogen giving the lower field signal will be referred to as H-6 and the one giving the upper field signal as H-6′. The signals of H-6 and H-6′ yield the following coupling constants: $J_{6,6'}$ = 16 Hz, $J_{NH,6}$ = 4 Hz, and $J_{NH,6'}$ = 8.6 Hz. The difference of coupling constants between the ammonium proton and the two diastereotopic C-6 hydrogens is of importance in the assignment of configuration to epimer **5a** (*vide infra*). The spectrum of **5a** in trifluoroacetic acid has the same pattern as in formic acid (Table I)

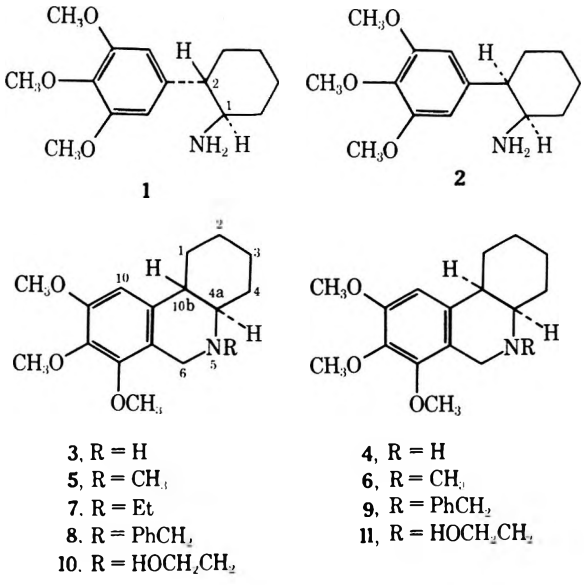
(1) This investigation was supported by Grant MH 12204 from the National Institute of Mental Health, U. S. Public Health Service. The compounds were submitted to Eli Lilly and Co. for pharmacological evaluation.

(2) W. F. Trager and A. C. Huitric, *J. Pharm. Sci.*, **54**, 1552 (1965).

TABLE I
60-MHz NMR SPECTRAL DATA OF HYDROCHLORIDE SALTS

Solvent	Compd	Chemical shifts, τ (ppm) H-10	H-6	H-6′	NCH_3	NH	$J_{NH,6}$	$J_{NH,6'}$
HCOOH	3 (trans)	3.13		~5.5[a]				
	5a (trans)	3.15	5.29	5.68	6.83		4.0	8.6
	5a, 5b equil[b]	3.15	5.3	5.7	6.83			
				~5.4[a]	7.02			
	4 (cis)	3.18		~5.4[a]				
	6a (cis)	3.19	5.25	5.74	6.80		4.2	7.2
	6a, 6b equil[b]	3.19						
		3.07		Complex	6.78			
CF_3COOH	5a	3.19	5.14	5.74	6.80	2.1	3.9	7.4
	6a	3.19	5.15	5.73	6.80	2.1	3.8	8.2
$CDCl_3$	5a, 6b equil[b]	3.40	5.5	6.0	7.07	−2.25	~4.0	~8.0
		3.37		~5.75[a]	7.28	−2.72		

[a] Near equivalence of H-6 and H-6′. [b] Values from equilibrated systems.



3, R = H
5, R = CH_3
7. R = Et
8. R = $PhCH_2$
10. R = $HOCH_2CH_2$

4, R = H
6, R = CH_3
9, R = $PhCH_2$
11, R = $HOCH_2CH_2$

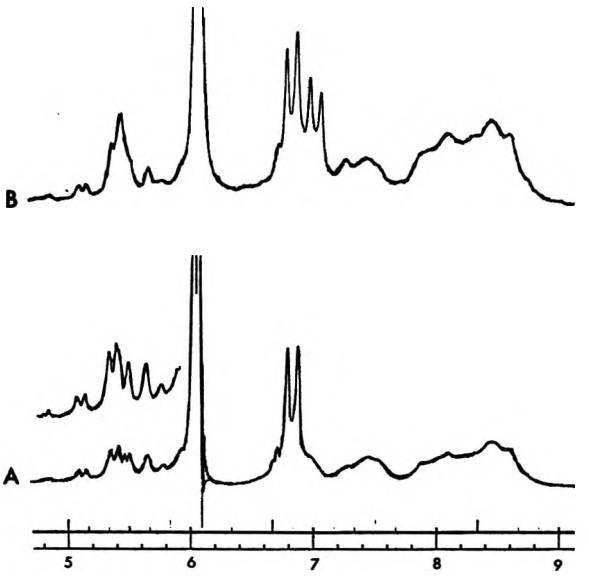


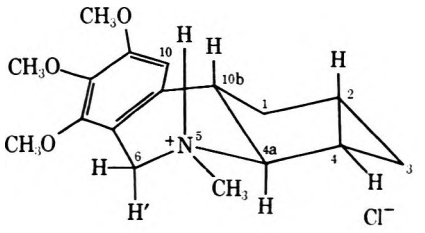
Figure 1.—Nmr spectra (60 MHz) of **5** HCl in 99% formic acid; spectrum A is prior to equilibration and B is after equilibration catalyzed by sodium formate.

but in addition it allows the detection of the signal of the ammonium proton as a broad signal at τ 2.1. Decoupling of the ammonium proton by strong irradiation at τ 2.1 caused a collapse of the *N*-methyl doublet to a singlet at τ 6.83 and it reduced the signals of H-6 and H-6′ to doublets ($J_{6,6'}$ = 16 Hz), thus confirming the assigned vicinal CH–NH^+ coupling.

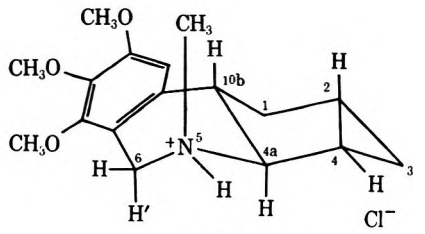
Spectrum B shows that the signal of the *N*-methyl group at τ 7.02 is at higher field for the minor epimer **5b** and that the chemical shifts of the C-6 hydrogens are more nearly equivalent, as seen from an enhancement of the signal in the region of τ 5.4. There is also a difference in the chemical shift of the aromatic hydrogen H-10 in the two epimers, τ 3.15 for **5a** and τ 3.13 for **5b**. The ratio of **5a** to **5b** is about 2:1 at equilibrium in formic acid. In the absence of sodium formate the equilibration required about one month at room temperature. In the presence of 2 equiv of sodium formate the equilibrium was reached in ~4 hr. Regeneration of the base from the equilibrated salt gave an nmr spectrum identical with that of the original base.

In deuterated chloroform, equilibration of the hydrochloride salt of **5** was established in less than 4 min, giving about equal amounts of the two epimers. An important feature of the spectrum is the presence of two ammonium proton signals of about equal intensities but of different widths which, taken together, integrate for one proton. The downfield signal at τ −2.72 has a width of about 15 Hz at 60 MHz and that at −2.25 is about 22 Hz wide. Irradiation of each NH^+ signal, in turn, decoupled only one NCH_3 doublet at a time, and showed that the low field NH^+ and the high field *N*-methyl signals are coupled, and vice versa. Equilibration between **5a** and **5b** in chloroform is fairly fast on an absolute time scale but still slow on the nmr time scale. The nmr spectrum of the hydrochloride salt of **5** in D_2O gives only one singlet for the *N*-methyl signal. This is indicative that in D_2O proton exchange and nitrogen inversion are fast processes on the nmr time scale and that the chemical shift of the *N*-methyl signal represents the weighted average of the shifts of the two epimers.

Configuration and Conformation of Salts 5a and 5b.—In the 4a,10b-trans compounds there is only one possible half-chair conformation of the hetero ring. A boat conformation is not ruled out *a priori*, but the nmr data are consistent with structures in which both **5a** and **5b** have the cyclohexane and hetero rings in chair and half-chair conformations, respectively (structures **5a** and **5b**), and where epimerization involves an inversion of the nitrogen with the methyl group occupying an equatorial position (cis to H-4a) in **5a** and an axial position (trans to H-4a) in **5b**. This assignment



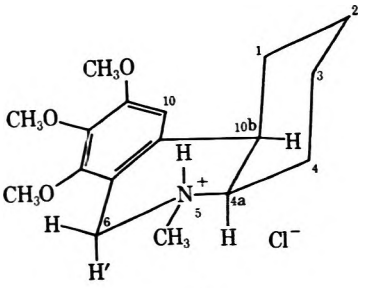
5a



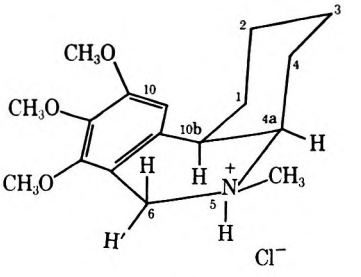
5b

is supported by the observed chemical shifts and splitting patterns of the signals of H-6 and H-6′, based on the demonstrated dependency of CH–NH$^+$ spin–spin coupling constants on dihedral angle in a manner similar to the coupling between vicinal protons on carbon atoms.[3,4] The observed coupling constant for **5a** in formic acid of $J_{NH,6'}$ = 8.6 Hz and $J_{NH,6}$ = 4 Hz are consistent with the NH proton having an axial orientation and H-6′ and H-6 having pseudoaxial and pseudoequatorial orientations, respectively. The upfield chemical shift of H-6′ is also consistent with this assignment. For the hydrochloride salt of the corresponding secondary amine (**3**) under similar conditions, the chemical shifts of the C-6 hydrogens are nearly equivalent. The effect of the N–CH_3 bond will be to shield the C-6 hydrogen having a cis orientation to the *N*-methyl group.[3,5] The more nearly equivalent chemical shifts of H-6 and H-6′ in **5b** is consistent with this shielding effect of the *N*-methyl group where H-6 is shielded by the *N*-methyl group relative to H-6′. The higher field position of the signal of the methyl group in **5b** also supports the assigned structures. The effect of the magnetic anisotropy of the aromatic ring will be to deshield the in-plane methyl group in **5a** relative to the out-of-plane methyl in **5b**. If epimer **5b** had a predominance of the boat conformation, the methyl group would occupy an analogous position relative to the aromatic ring as in **5a**. The assigned structures are also confirmed by the nonequivalent ammonium proton signals in chloroform. Decoupling experiments showed that the lower field, narrower signal belongs to epimer **5b**. This is consistent with the assigned structures on the basis of shielding effects of the aromatic ring and of larger coupling constants in **5a** between the axial NH proton with axial H-4a and pseudoaxial H-6′ hydrogens than between the equatorial NH proton and the same adjacent hydrogens in **5b**.

Configuration and Conformation of Salts 6a and 6b.— In the 4a,10b-cis compounds there are two possible half-chair conformations of the hetero ring, each being associated with a given chair conformation of the



6a



6b

cyclohexane ring. The nmr spectrum of freshly prepared formic acid solution of crystalline hydrochloride salt of **6** is consistent with a single epimeric form (structure **6a**). The spectrum is characterized by well-defined sets of doublets of doublet for the diastereotopic hydrogens on C-6 at τ 5.25 and 5.74, one doublet for the *N*-methyl signal at 6.80, a single signal for H-10 at 3.19, and a fairly narrow envelope (<1.0 ppm) for the eight methylene protons on carbons 1–4. The coupling constants associated with H-6 and H-6′ are $J_{6,6'}$ = 16 Hz, $J_{NH,6}$ = 4.2 Hz, and $J_{NH,6'}$ = 7.2 Hz. The same pattern is obtained in trifluoroacetic acid. The spectra are consistent with structure **6a** where the hetero ring has a half-chair conformation and the ammonium proton has an axial orientation and is coupled with pseudoaxial H-6′ and pseudoequatorial H-6. The similarity of the chemical shift of the *N*-methyl group with that of **5a** implies an analogous orientation relative to the aromatic ring. The narrowness of the combined cyclohexane methylene signals implies that the hydrogens on C-1 do not fall in the deshielding region of the aromatic ring as is the case in **5a** and **5b** where their signals experience a downfield shift and are centered at about τ 7.4 (Figure 1). Equilibration in formic acid caused the appearance of a second aromatic H-10 signal at τ 3.07, an increase in the complexity of the H-6 and H-6′ signals, and a broadening of the envelope of the cyclohexane methylene signals. There was no appearance of a second *N*-methyl signal. The ratio of **6a** to **6b**, as obtained from the integration of the H-10 signals at equilibrium, was about 3:2. The results are consistent with structures **6a** and **6b**, each having the chair and half-chair conformations of the cyclohexane and hetero ring, respectively. In the thermodynamically most stable epimer (**6a**) H-4a has an equatorial orientation in relationship to the cyclohexane ring and an axial orientation with respect to the half-chair hetero ring and the *N*-methyl group is equatorial and cis to H-4a. Epimerization is associated with an inversion of conformation of the cyclohexane and the hetero ring to give structure **6b** where H-4a is axial in relationship to the cyclohexane ring and equatorial relative to the half-chair hetero ring and where the *N*-methyl group

(3) H. Booth and J. H. Little, *Tetrahedron*, **23**, 291 (1967).

(4) (a) J. L. Sudmeier and G. Occupanti, *J. Amer. Chem. Soc.*, **90**, 154 (1968); (b) H. Booth, *Chem. Commun.*, 802 (1968); (c) J. I. Legg and D. W. Cooke, *Inorg. Chem.*, **5**, 594 (1966).

(5) H. P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Lett.*, 2553 (1964).

is trans to H-4a but still occupies an equatorial orientation and has the same relative position to the aromatic ring, thus accounting in part for the identical chemical shifts of the *N*-methyl group in the two epimers. In **6b** the equatorial hydrogen on C-1 falls close to, and in the field of deshielding of, the aromatic ring.

Nmr Spectra and Conformation of Bases in the Trans and Cis Series.—The nmr spectra of the free bases of the 4a,10b-trans series, measured in deuteriochloroform and in pyridine, are consistent with structures having the cyclohexane and hetero rings in chair and half-chair conformations, respectively, and with a predominance of the structure where the N substituent occupies an equatorial orientation. For the secondary amine (**3**) the difference in chemical shift of the diastereotopic hydrogens 6 and 6′ is 0.16 ppm in chloroform and 0.20 ppm in pyridine. N-Alkylation brings a difference of about 0.7 ppm and the increase in nonequivalence is associated primarily with an upfield shift of the signal of H-6′. A shielding of the pseudoaxial H-6′ is expected by the *N*-alkyl bond when the *N*-alkyl group occupies an equatorial orientation on the half-chair hetero ring. This shielding parallels the pattern produced by alkylation of 4-methylpiperidine.[3] The geminal coupling $J_{6,6'}$ was found to be in the order of 16 Hz for the secondary and tertiary amine of the trans and cis series with the exception of the *N*-benzyl compounds where it was closer to 13 Hz. For compounds **5** and **7** the signal of H-6′ appears as doublets of doublet, $J_{6',6}$ = 16 Hz and J = 1.5 Hz. The small coupling is attributed to long-range coupling by H-4a. Examples of H–C–N–C–H coupling are known,[6,7] and, although the proposed geometry does not satisfy the planar requirement of the W rule in the H–C–C–C–H system,[8] the stereochemistry is analogous to that of a carbocyclic steroid in which long-range coupling has been reported through a nonplanar H–C–C–C–H system.[9] In the spectrum of **5** in pyridine the signals of H-4a and H-10b partially overlap with each other but centers of individual signals appear to be at about τ 7.4 and 7.6. Irradiation at τ 7.4 caused the four-peak multiplet of H-6′ to collapse to a doublet, $J_{6,6'}$ = 15.6 Hz. No decoupling occurred upon irradiating at τ 7.6. This supports the long-range coupling by H-4a because in every case where differentiation has been possible between the signals of H-4a and H-10b the former was found to be at lower field. No similar long-range coupling was observed in any of the cis isomers.

The spectra of the cis isomers show a nonequivalence of chemical shifts of H-6 and H-6′ and an upfield shift of the signal of H-6′ upon N-alkylation similar to what was seen for the trans compound. In addition, the signals of H-4a and H-10b in **4** are well separated in both solvents. In pyridine one signal occurs at τ 6.9 as a fairly narrow signal, $W_{1/2} \sim 7$ Hz, and the other as a wider unresolved multiplet at τ 7.5. In the methylated product **6** the narrow signal has been shifted upfield and the two signals overlap at about τ 7.6, and there has also been a similar upfield shift of 0.67 ppm of the signal of H-6′. The data suggest that the narrow signal at τ 6.9 is caused by H-4a having a similar relative position to the *N*-methyl group as H-6′ and that both these hydrogens are cis to the *N*-methyl group. The relative widths of the signal of H-4a and H-10b implies a chair conformation of the cyclohexane ring where H-10b is axial and H-4a is equatorial, for **4** as well as **6**. This conclusion is supported by the narrow range of the signals of the cyclohexane methylene hydrogens, which demonstrates the absence of deshielding of hydrogens on C-1 and indicates a structure where the C-10b–C-1 bond is perpendicular to the plane of the aromatic ring. The combined data are consistent with **6** having a predominance of the structure in which the hetero and cyclohexane rings have half-chair and chair conformations, respectively, where H-4a occupies an axial orientation with respect to the hetero ring and an equatorial orientation relative to the cyclohexane ring, and where the *N*-methyl group is equatorial and cis to H-4a. It is interesting to note that this is also the geometry of the thermodynamically most stable protonated form of **6**.

(6) D. H. R. Barton, R. H. Hesse, and G. W. Kirby, *J. Chem. Soc.*, 6379 (1965).

(7) T. Masamune, S. Ohuchi, S. Shimokawa, and H. Booth, *Tetrahedron*, **22**, 773 (1966).

(8) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 334.

(9) Y. Osawa and M. Neeman, *J. Amer. Chem. Soc.*, **85**, 2856 (1963).

Experimental Section

Melting points were determined on a Kofler hot stage unless otherwise indicated. The salts in the 7,8,9-trimethoxy-1,2,3,4,-4a,5,6,10b-octahydrophenanthridine series decomposed on heating and as a result melting points are a relatively poor criterion of purity. Most uniform results were obtained by placing samples on the hot stage within about 5–10° of the melting point. Owing to heat sensitivity it was also necessary to dry analytical samples at room temperature. Elemental analyses were performed by Alfred Bernhardt, Mülheim, Germany, and Huffman Laboratories, Wheatridge, Colo. Nmr spectra were recorded on Varian A-60 or Varian T-60 spectrometers operating at 33–35° with tetramethylsilane internal reference. Equilibrium studies were carried out at room temperature with periodic examination by nmr. Table I lists the nmr data for the hydrochloride salts. Ir spectra were determined on Beckman IR-5a or Beckman IR-20 spectrophotometers. Solid samples were determined in the solid phase as KBr pellets unless otherwise indicated. Strong methoxy absorption at 1110–1130 cm^{-1} was present in all compounds.

7,8,9-Trimethoxy-4a,10b-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (3).—A solution of 453 mg of 1 hydrochloride[2] (1.50 mmol) and 146 mg (~1.63 mmol) of aqueous 37% formaldehyde in 30 ml of ethanol was refluxed for 29 hr. The reaction mixture, from which considerable crystalline product had separated, was evaporated and the resulting crude solid crystallized from methanol, yielding 449 mg (95.2%) of **3** hydrochloride as colorless needles or plates, mp 262.5–263.5° dec, ir 2790 cm^{-1} (NH^+).

Anal. Calcd for $C_{16}H_{24}O_3NCl$: C, 61.23; H, 7.71; N, 4.46. Found: C, 61.54; H, 7.51; N, 4.51.

The amine **3** regenerated from the hydrochloride after crystallization from hexane–benzene had mp 76–78°; ir 3440 cm^{-1} (NH); nmr ($CDCl_3$) τ 3.36 (s, 1, H-10), 5.87 (d, 1, $J_{6,6'}$ = 16 Hz, H-6), 6.03 (d, 1, $J_{6,6'}$ = 16 Hz, H-6′), 8.51 (s, 1, NH).

The *p*-toluenesulfonate was prepared by addition of *p*-toluenesulfonic acid to a methanolic solution of **3** followed by removal of methanol under reduced pressure. Two crystallizations from methanol–water gave the hydrate, mp <100° with resolidification and remelting at 158.5–159.5° (Fisher-Johns). Azeotropic removal of water of hydration with chloroform followed by ethyl acetate crystallization afforded the salt as colorless needles, partially melting at 157.5–160°, regrowth to cubes at 160–167°, and complete melting by 169.5°. The melting behavior is probably a result of a mixture of polymorphic forms. Infrared NH^+ absorption occurred at 2800 cm^{-1}.

7,8,9-Trimethoxy-4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (4).—Treatment of 9.66 g (32.0 mmol) of **2** hydrochloride[2] with ~42 mmol of formaldehyde in 650 ml of refluxing ethanol for 24 hr afforded 9.93 g (98.8%) of **4** hydro-

chloride after crystallization from 2-propanol, mp 244–244.5° dec, ir 2780 cm^{-1} (NH^+).

Anal. Calcd for $C_{16}H_{24}O_3NCl$: C, 61.23; H, 7.71; N, 4.46. Found: C, 61.07; H, 7.54; N, 4.39.

The amine **4** crystallized from hexane and had mp 90.5–92.5°; ir 3440 cm^{-1} (NH); nmr ($CDCl_3$) τ 3.56 (s, 1, H-10), 5.85 (d, 1, $J_{6,6'}$ = 16.5 Hz, H-6), 6.08 (d, 1, $J_{6',6}$ = 16.5 Hz, H-6'), 8.46 (s, 1, NH).

5-Methyl-7,8,9-trimethoxy-4a,10b-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (5).—With cooling, 0.88 g of 88% formic acid (~16.8 mmol) was added to 1.061 g of **1** (4.00 mmol). Aqueous 37% formaldehyde (1.0 g, ~12.3 mmol) was added and the mixture was heated until gas evolution started. After vigorous gas evolution had subsided, heating on a steam bath was resumed overnight (total 18 hr). After cooling, the mixture was diluted with a small amount of water (2 ml), chilled, and made alkaline with KOH with stirring. The amine liberated was extracted with benzene (three 50-ml portions). The benzene extracts were dried (Na_2SO_4) and evaporated, giving the crude liquid amine. Conversion to the hydrochloride and crystallization from 2-propanol–ethyl acetate yielded 1.247 g (95.1%) of **5** hydrochloride, mp 209–210° dec, ir 2490 cm^{-1} (NH^+).

Anal. Calcd for $C_{17}H_{26}O_3NCl$: C, 62.28; H, 8.00; N, 4.27. Found: C, 61.99; H, 7.76; N, 4.26.

The liquid amine **5** regenerated from hydrochloride exhibited moderately strong absorption in the ir (liquid, neat) at 2760 cm^{-1} (NCH); nmr ($CDCl_3$) τ 3.43 (s, 1, H-10), 6.06 (d, 1, $J_{6,6'}$ = 15.6 Hz), 6.71 (d d, 1, $J_{6',6}$ = 15.6 Hz, $J_{6',4a}$ = 1.5 Hz, H-6'), 7.63 (s, 3, NCH_3).

The *p*-toluenesulfonate prepared as described for that of **3** above was freed of traces of *p*-toluenesulfonic acid by extraction of a benzene solution with water. The benzene extracts were dried (Na_2SO_4) and evaporated. Treatment with a small amount of ethyl acetate afforded crystals which on recrystallization from benzene–petroleum ether (bp 30–60°) gave needles, mp 171–172.5°, ir 2570 cm^{-1} (NH^+).

5-Methyl-7,8,9-trimethoxy-4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (6).—A solution of 1.57 g (5.65 mmol) of **4** and 5.0 ml of 37% formaldehyde in 100 ml of ethanol was hydrogenated in the presence of 500 mg of 10% Pd/C until hydrogen uptake ceased. Following removal of catalyst by filtration, the solution was treated with 5 ml of glacial acetic acid and evaporated. The residue was dissolved in 10 ml of water, chilled, and made alkaline with KOH. The liberated amine was extracted with benzene (four 50-ml portions) and the benzene extracts were dried (Na_2SO_4) and evaporated. The crude liquid amine was converted to the hydrochloride in the usual manner; crystallization from 2-propanol–ethyl acetate afforded 1.715 g (92.5%) of **6** hydrochloride, mp 204–206.5° dec, ir 2550 cm^{-1} (NH^+).

Anal. Calcd for $C_{17}H_{26}O_3NCl$: C, 62.28; H, 8.00; N, 4.27. Found: C, 62.34; H, 7.92; N, 4.20.

Clark–Eschweiler treatment of **2** as described for preparation of **5** afforded **6** hydrochloride in 84.9% yield. Physical and spectral properties of this product were identical with those of a sample prepared by the catalytic reductive methylation above.

Nmr of free base in $CDCl_3$: τ 3.53 (s, 1, H-10), 6.08 (d, 1, $J_{6,6'}$ = 15.8 Hz, H-6), 6.70 (d, 1, $J_{6',6}$ = 15.8 Hz, H-6'), 7.58 (s, 3, NCH_3).

5-Ethyl-7,8,9-trimethoxy-4a,10b-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (7).—Catalytic reductive alkylation of 2.08 g (7.50 mmol) of **3** using excess acetaldehyde (~3.31 g, ~75 mmol) according to the procedure described for **6** followed by crystallization from 2-propanol yielded 2.20 g (85.9%) of **7** hydrochloride as a microcrystalline solid, mp 210–210.5° dec, ir 2500 cm^{-1} (NH^+).

Anal. Calcd for $C_{18}H_{28}O_3NCl$: C, 63.24; H, 8.26; N, 4.10. Found: C, 63.17; H, 8.29; N, 4.24.

Nmr of free base in pyridine: τ 3.24 (s, 1, H-10), 5.83 (d, 1, $J_{6,6'}$ = 16.2 Hz, H-6), 6.43 (d d, 1, $J_{6',6}$ = 16.2 Hz, $J_{6',4a}$ = 1.5 Hz, H-6'), 7.40 (q, 2, NCH_2CH_3), 8.94 (t, 3, NCH_2CH_3).

5-Benzyl-7,8,9-trimethoxy-4a,10b-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (8).—A mixture of 277 mg (1.00 mmol) of **3**, 186 mg (4.0 mmol) of 99% formic acid, and 227 mg (2.14 mmol) of redistilled benzaldehyde was heated under reflux on a steam bath for 18 hr. Moderate to slow gas evolution occurred initially, but abated considerably after 2 hr. After cooling, the mixture was diluted with 5 ml of glacial acetic acid and 10 ml of 5% HCl. Excess benzaldehyde was removed by washing with carbon tetrachloride (three 5-ml portions). Carbon tetrachloride washings were extracted with an additional 10 ml of 5% HCl. Aqueous acidic solutions deposited some of the product hydrochloride on standing; resolubilization was effected by addition of methanol. The aqueous acidic portions were combined and evaporated under reduced pressure. Crystallization of the residue from methanol yielded 313 mg (77.5%) of the hydrochloride of **8** as colorless needles, mp 209–210° dec, ir 2500 cm^{-1} (NH^+).

Anal. Calcd for $C_{23}N_{30}O_3NCl$: C, 68.38; H, 7.49; N, 3.47. Found: C, 68.09; H, 7.55; N, 3.56.

5-Benzyl-7,8,9-trimethoxy-4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (9).—Heating of 1.387 g (5.00 mmol) of **4** with formic acid and benzaldehyde for 7 hr as described above and crystallization from ethyl acetate and 2-propanol produced 1.561 g (77.2%) crude **9** hydrochloride, mp 181–190° dec (Fisher-Johns). A pure sample crystallized from ethanol melted at 182.5–183° dec to a two-phase system, ir 2510 cm^{-1} (NH^+).

Anal. Calcd for $C_{23}H_{30}O_3NCl$: C, 68.38; H, 7.49; N, 3.47. Found: C, 67.99; H, 7.52; N, 3.70.

Nmr of free base in pyridine: τ 3.25 (s, 1, H-10), 5.93 (d, 1, $J_{6,6'}$ = 13 Hz, H-6), 6.50 (d, 1, $J_{6',6}$ = 13 Hz, H-6'), 6.2 (s, 2, NCH_2Ph). In $CDCl_3$ the signals of the benzylic hydrogens are nonequivalent and they overlap with the signals of the methoxy groups.

5-(2-Hydroxyethyl)-7,8,9-trimethoxy-4a,10b-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (10).—A solution of 838 mg (3.02 mmol) of **3** and ~5 mmol of ethylene oxide in 30 ml of absolute ethanol was heated at 75° in a small stainless steel Parr bomb for 24 hr. After cooling, the contents of the bomb were evaporated. Crystallization of the residue from acetone, then acetone–hexane, afforded 757 mg (77.9%) of **10**, mp 118.5–120.5° (Fisher-Johns). A sample purified for analysis by two further crystallizations from acetone followed by recrystallization from benzene–hexane had mp 120–121.5°; ir ($CHCl_3$) 3620 (w), 3420 cm^{-1} (OH); nmr (pyridine) τ 3.21 (s, 1, H-10), 5.68 (d, 1, $J_{6,6'}$ = 16.4 Hz, H-6), 6.22 (d, 1, $J_{6',6}$ = 16.4 Hz, H-6'), 6.1 (m, 2, $NHCH_2CH_2OH$), 7.13 (m, 2, $NHCH_2CH_2OH$).

Anal. Calcd for $C_{18}H_{27}O_4N$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.51; H, 8.58; N, 4.60.

The hydrochloride was prepared by treatment with 5% hydrochloride acid and isolated by chloroform extraction as described below for **11** hydrochloride. Crystallization from acetone gave colorless needles: mp 170.5–172° dec; ir 3330 (OH), 2530 cm^{-1} (NH^+).

5-(2-Hydroxyethyl)-7,8,9-trimethoxy-4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (11).—Hydroxyethylation of 693 mg (2.50 mmol) of **4** with ~6.2 mmol of ethylene oxide in 50 ml of absolute ethanol was carried out under the conditions employed for the *trans* isomer **10**. Evaporation of the reaction mixture gave crude **11** as a viscous oil which failed to crystallize. It was converted to the hydrochloride by shaking a benzene solution with 5% HCl (20 ml in three portions). The hydrochloride salt was extracted from the combined acid extracts with chloroform (50 ml total) and the chloroform extracts were dried (Na_2SO_4) and evaporated. Crystallization of the residue from acetone afforded 723 mg (80.7%) of **11** hydrochloride: mp 172–174° dec (Fisher-Johns); ir 3320 (OH), 2590 cm^{-1} (NH^+). An analytical sample prepared by three crystallizations from 2-propanol–ethyl acetate had mp 172.5–177.5° dec, with the melting point very dependent on heating rate.

Anal. Calcd for $C_{18}H_{28}O_4NCl$: C, 60.41; H, 7.89; N, 3.92. Found: C, 60.02; H, 7.92; N, 4.21.

Registry No.—**3**, 34035-48-8; **3** HCl, 34035-49-9; **3** tosylate, 34035-50-2; **4**, 34035-51-3; **4** HCl, 34035-52-4; **5**, 34035-53-5; **5** HCl, 34035-54-6; **5** tosylate, 34035-55-7; **6**, 34035-56-8; **6** HCl, 34035-57-9; **7**, 34035-58-0; **7** HCl, 34087-66-6; **8** HCl, 34035-59-1; **9**, 34035-60-4; **9** HCl, 34035-61-5; **10**, 34087-67-7; **10** HCl, 34035-62-6; **11** HCl, 34035-63-7.

Synthesis of 1,2- and 1,4-Dihydropyridines

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N-Carbomethoxy-1,2- and -1,4-dihydropyridine (1 and 2) have been prepared by the reaction of methyl chloroformate with pyridine in the presence of sodium borohydride. These compounds have been shown to be useful derivatives for the synthesis of other heterocycles and study of the dihydropyridine ring system. Reduction of 1 and 2 with $LiAlH_4$ gave the *N*-methyl derivatives. Treatment of 2 with methyllithium gave the unsubstituted dihydropyridine 7, whereas a similar treatment of 1 gave a complex mixture of products. Photolysis of 1 gave *N*-carbomethoxybicyclo[2.2.0]hex-5-ene.

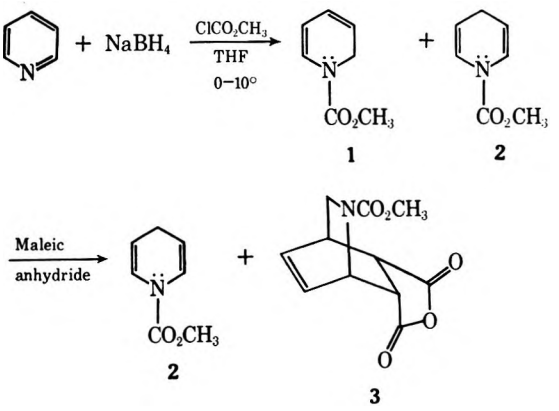
The 1,4- and 1,3-cyclohexadienes have proven to be extremely valuable intermediates in organic synthesis. The corresponding heterocycles, 1,2- and 1,4-dihydropyridine, should also prove valuable for the preparation of interesting heterocyclic compounds. In addition, the 1,4-dihydropyridine ring system is of biological importance since it occurs in the reduced forms of nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH).[1] In contrast to the carbocycles, studies on the *simple* derivatives of the heterocycles have been hindered by their susceptibility to oxidation and the lack of convenient methods for their preparation.

A large number of substituted 1,2- and 1,4-dihydropyridines have been prepared by cyclization reactions (Hantzsch ring closure) and by reduction of pyridinium ions.[2] The Hantzsch ring closure works well only for the preparation of highly substituted dihydropyridines. Except in a few cases,[3] the reduction of pyridinium ions is successful only if strong electron-withdrawing groups are present on the pyridine ring.[4]

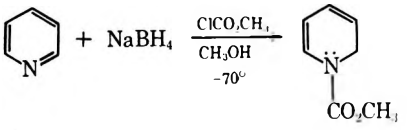
An elegant synthesis of the 1-trimethylsilyl-substituted 1,2- and 1,4-dihydropyridines has recently been accomplished by Cook and Lyons.[5] These compounds would appear very valuable derivatives for further study of the dihydropyridine structure. Unfortunately, any extensive study of these ring systems is hindered by the small quantity of 1,2 isomer produced, their instability, and by the tedious separation procedure required (vapor phase chromatography).

We report that both *N*-carbomethoxy-1,2- and -1,4-dihydropyridine can be produced by treating a mixture of pyridine and sodium borohydride with methyl chloroformate. Although this reaction can be carried out in a number of solvents (ether, glyme, tetrahydrofuran, methanol, and water), tetrahydrofuran proved to be the solvent of choice.

Carrying out the reaction in tetrahydrofuran and maintaining the temperature below 10° gave a mixture of the dihydropyridines containing about 35–40% of the 1,4 isomer. These can be separated on a small scale using either preparative layer chromatography (silica gel) or gas phase chromatography (5% SE-30 on Chrom G). This is not a convenient procedure for the preparation of large quantities of these pure dihydropyridines. However, large quantities of the pure 1,4-dihydropyridine can be obtained by simply treating the reaction mixture with maleic anhydride. The 1,2-dihydropyridine readily reacts to give a Diels–Alder adduct which can easily be removed by washing with 15% sodium hydroxide.



The amount of 1,4 isomer can be reduced substantially 2–4% by carrying out the reaction in methanol using a Dry Ice–acetone cooling bath.



The structures of these dihydropyridines are clearly evident from their spectral data[5] and their chemical conversion to known dihydropyridines (see below).

The *N*-carbomethoxydihydropyridines are very useful derivatives of the dihydropyridine ring system for several reasons. The carbomethoxy substituent stabilizes the dihydropyridine structure, causing these compounds to be more resistant to air oxidation than simple *N*-alkyl derivatives and therefore they can be handled relatively easily in the laboratory. However, even these dihydropyridines will decompose when exposed to atmospheric oxygen at room temperature for prolonged periods, although they can be stored indefinitely under argon at −30°. Because of the resonance interaction of the lone pair on nitrogen with the carbonyl group, the carbon–carbon double bonds of these dihydropyridines have little enamine character. For example, they are reasonably stable to aqueous solutions of mineral acids.

The carbomethoxy substituent is also a versatile

(1) S. P. Colowich, J. van Eys, and J. H. Park in "Comprehensive Biochemistry," Vol. 14, M. Florkin and E. H. Stotz, Ed., Elsevier, Amsterdam, 1966, Chapter 1.

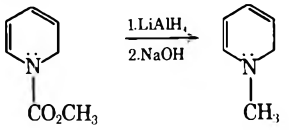
(2) A. Albert, "Heterocyclic Chemistry," 2nd ed, The Athlone Press, London, 1968, p 303 ff.

(3) The nmr spectra are similar to those previously reported for *N*-phenyl-1,2- and 1,4-dihydropyridine: M. Sanders and E. H. Gold, *J. Org. Chem.*, **27**, 1439 (1962).

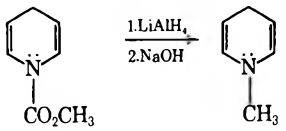
(4) P. S. Anderson and R. E. Lyle, *Tetrahedron Lett.*, 153 (1964).

(5) N. C. Cook and J. E. Lyons, *J. Amer. Chem. Soc.*, **88**, 3396 (1966).

functional group in organic synthesis. It can either be converted to a hydrogen-substituted derivative or reduced to a *N*-methyl group, which is a common functionality in natural products. For example, we have observed that treatment of these dihydropyridines with lithium aluminum hydride gives the relatively unstable *N*-methyl derivatives. The physical properties of **4** are consistent with those previously reported,[6] whereas **5** is a new compound.



1 4



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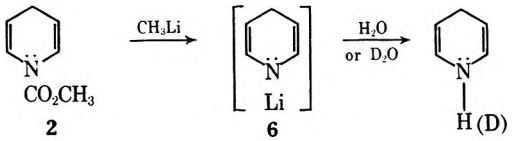
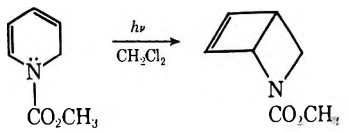
Treatment of 1,4-dihydropyridine **2** with methyllithium gave the lithio derivative **6**. This was not isolated, but treatment with either water or deuterium oxide produced the 1,4-dihydropyridine.[7] Dihydropyridine **7** is remarkably stable. It shows no tendency to decompose, isomerize, or undergo exchange of the hydrogens β to the nitrogen when treated with deuterium oxide in acetone-d_6 for several days.



2 6 7

Preliminary studies have indicated that these heterocycles are very useful for the preparation of interesting heterocyclic compounds. For example, photolysis of 1,2-dihydropyridine **1** in methylene chloride provides a very convenient synthesis to the 2-azabicyclo[2.2.0]-hex-5-ene ring system.



1 8

Experimental Section[8]

N-**Carbomethoxy-1,4-dihydropyridine** (**2**).—Methyl chloroformate (47.3 g, 0.5 mol) was added to 10 g of $NaBH_4$ and 39.4 g (0.5 mol) of pyridine in 200 ml of THF cooled in an acetone–ice bath at a rate so that the reaction temperature did not exceed 10°. The reaction mixture was stirred for an additional 1.4 hr and enough H_2O (*ca.* 400 ml) was added to dissolve the inorganic salts. The reaction mixture was extracted with ether. The ethereal extracts were combined, washed with water, dried ($MgSO_4$), and evaporated *in vacuo* at *ca.* 40° to give *ca.* 36 g of the mixture of dihydropyridines. The pure 1,4 isomer (*ca.* 10 g) was obtained by treating this mixture with 50 g of maleic anhydride and 200 ml of CH_2Cl_2 (previously purged with N_2) and refluxed for 14 hr. The solvent was evaporated (*in vacuo*), and the residue was dissolved in ether and washed with 15% NaOH until colorless. The ethereal layer was dried ($MgSO_4$) and removed *in vacuo*. Further purification of the 1,4-dihydropyridine **2** can be effected by passing it through basic alumina with ether. This produces the dihydropyridine as a clear, mobile liquid of >97% purity: nmr ($CDCl_3$) τ 3.42 (d, broad, 2 H, J = 7.5 Hz, NCH=), 5.05–5.40 (m, 2 H, NCH=CH), 6.32 (s, 3 H, OCH_3), and 7.05–7.33 (m, 2 H, CH_2); ir (CCl_4) 1726 (C=O) and 1634 cm^{-1} (C=C); uv max (hexane) 224 nm (ϵ 13,700).

N-**Carbomethoxy-1,2-dihydropyridine** (**1**).—Methyl chloroformate (18.2 g, 0.2 mol) in 25 ml of ether was added to 8.0 g of sodium borohydride and 15.8 g (0.20 mol) of pyridine in 75 ml of absolute methanol cooled in Dry Ice–acetone. The rate of addition was controlled so that the temperature of the reaction mixture did not exceed −69°. The reaction mixture was stirred for an additional 1.5 hr and was then poured into ice water. Enough water was added to dissolve the inorganic salts and the mixture was extracted with ether (*ca.* 300 ml). These were combined, washed thoroughly with water, and dried ($MgSO_4$). Removal of the solvent *in vacuo* (*ca.* 50°) gave *ca.* 18 g of the 1,2-dihydropyridine **1**. Further purification can be effected by passing the product through basic alumina with ether: nmr (CCl_4) τ 3.47 (d, broad, 1 H, J = 7.5 Hz, NCH=), 4.05–5.18 (m, 3 H, olefinic), 5.85 (doublet of doublets, 2 H, J = 3.5, 2.0 Hz, CH_2), and 6.37 (s, 3 H, OCH_3); ir (CCl_4) 1718 (C=O), 1647 (C=C), and 1585 cm^{-1} (C=C); uv max (hexane) 302 nm (ϵ 3800).

N-**Methyl-1,2-dihydropyridine** (**4**).—To 2.40 g of $LiAlH_4$ in 50 ml of ether cooled in an ice bath was added 5.60 g of 1,2-dihydropyridine **1**. The reaction was allowed to warm to room temperature and stir for 3.25 hr. The reaction was worked up by decomposing the excess $LiAlH_4$ with 8.5 ml of 20% NaOH, filtering the inorganic salts, and removing the solvent *in vacuo* at room temperature (the dihydropyridine was maintained under argon at all times). This gave a quantitative yield of **4**: nmr (CCl_4) τ 4.08–4.47 (m, 2 H), 4.80–5.18 (m, 1 H), 5.37–5.67 (m, 1 H), 6.23 (d, broad, J = 3.5 Hz), and 7.43 (s, 3 H, NCH_3). The nmr spectrum of this sample proved to be the same as that of an authentic sample prepared independently.[6] The dihydropyridine was stored over KOH pellets at −30°.

N-**Methyl-1,4-dihydropyridine** (**5**).—To 2.40 g of $LiAlH_4$ in 50 ml of ether cooled in an ice bath was added over 10 min 5.60 g of *N*-carbomethoxy-1,4-dihydropyridine. The reaction mixture was allowed to warm to room temperature and was refluxed for 24 hr. The reaction mixture was cooled in an ice bath and the excess $LiAlH_4$ was decomposed with 8.5 ml of 20% NaOH. The salts were filtered and the ether was removed *in vacuo* at 25°, giving a 90% yield of **5** as a pale yellow liquid. The nmr spectrum showed the product to be >95% pure, but it could be further purified by molecular distillation (10^{-3} mm), giving **5** as a colorless liquid that was unstable to atmospheric oxygen: nmr ($CDCl_3$) τ 4.43 (doublet of triplets, J = 8.0 and 1.5 Hz, 2 H, NCH=), 5.58–5.88 (m, 2 H, NCH=CH), 7.00–7.23 (broad s, $W_{1/2}$ = 7.0 Hz, 2 H, CH_2) and 7.32 (s, 3 H, NCH_3); ir (CCl_4) 3065 (CH=) and 16.75 cm^{-1} (C=C); uv (hexane) 270 (ϵ 1220, shoulder) and 302 nm (ϵ 940, shoulder).

1,4-Dihydropyridine (**7**).—To 6 ml of 2 *M* methyllithium in 8 ml of dry ether (previously purged with N_2) cooled in an acetone–ice bath was added 560 mg of *N*-carbomethoxy-1,2-dihydropyridine. The reaction was stirred for 20 min and enough H_2O was added to dissolve the inorganic salts. The aqueous phase was separated and the organic layer was washed several times with water. The organic phase was dried ($MgSO_4$) and the solvent was removed with a stream of nitrogen at room temperature. All of the other above operations were carried out in an argon atmosphere.

The nmr spectrum (acetone-d_6) was virtually identical with that previously reported.[7] If the above reaction mixture is worked up with D_2O, then the multiplicity of the hydrogens α to the nitrogen is simplified. They occur as a broadened doublet (J = 8.0 Hz).

N-**Carbomethoxy-2-azabicyclo[2.2.0]hex-5-ene** (**8**).—A 5% solution of 1,2-dihydropyridine **1** was irradiated using a Rayonet photochemical reactor (RP-3000 lamps) until the nmr spectrum showed the consumption of all the starting material. Removal of the solvent gave an orange oil. The nmr spectrum showed this to be *ca.* 85% pure. Pure **8** (>95%) could be obtained by passing the crude product through basic alumina with ether: nmr ($CDCl_3$) 3.37–3.52 (m, 2 H, CH=CH), 5.17 (triplet of

(6) E. M. Fry, *J. Org. Chem.*, **29**, 1647 (1964).

(7) N. C. Cook and J. E. Lyons, *J. Amer. Chem. Soc.*, **87**, 3283 (1965).

(8) Analyses were performed by Gailbraith Laboratories, Knoxville, Tenn. The nmr spectra were recorded using a Varian A-60 spectrometer, the infrared spectra were recorded using a Perkin-Elmer 257 grating spectrometer, and the ultraviolet spectra were recorded using a Cary 14 spectrometer.

doublets, 1 H, J = 3.0, 1.5 Hz, bridgehead α to N), 5.83–6.67 (m, 3 H), and 6.32 (s, 3 H, OCH_3); ir (CCl_4) 1710 (C=O) and 1596 cm^{-1} (C=C). The analytical sample was further purified by glc (10 ft × 0.25 in. 5% SE-30 at 125°, retention time 60 min).

Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52. Found: C, 60.24; H, 6.54.

Registry No.—**1**, 33707-36-7; **2**, 33707-37-8; **4**, 33707-38-9; **5**, 33666-44-3; **8**, 33707-39-0.

Acknowledgment.—We are indebted to the National Science Foundation (GP-20099) for financial support of this work.

2,4-Diaminopyrimidines from Dicyandiamide. IV. Condensation with Bicyclic Aromatic Ketones[1,2]

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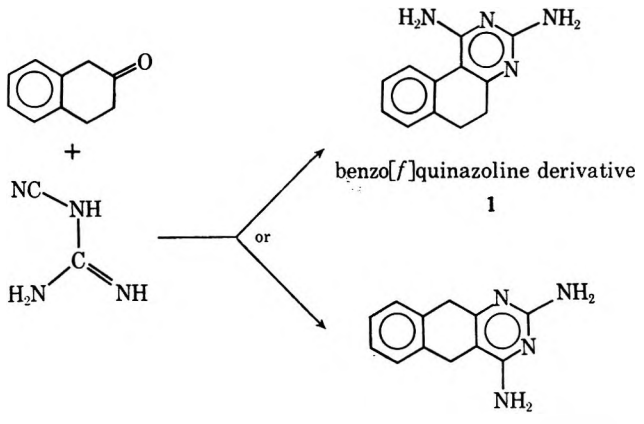
Received August 31, 1971

The synthesis of several tricyclic diaminopyrimidine derivatives by condensation of dicyandiamide with bicyclic aromatic ketones is reported. An interesting skeletal rearrangement was observed when 2,4-diaminobenzo[*g*]quinazoline (**5a**) was isolated as the major product of palladium–charcoal dehydrogenation (under disproportionation conditions) of 1,3-diamino-5,6-dihydrobenzo[*f*]quinazoline (**1**), the 2-tetralone/dicyandiamide condensation product. Representatives of the 2,4-diaminobenzo[*h*]quinazoline, the 2,4-diaminothieno[2,3-*h*]-quinazoline, and the 2,4-diamino-5*H*-indeno[1,2-*d*]pyrimidine ring systems are described.

In a program of synthesis of pyrimidine derivatives as potential folic acid antagonists and antitumor agents,[3] a number of 2,4-diaminopyrimidine ring systems have been synthesized in our laboratory by the direct, one-step condensation of dicyandiamide with ketones having an available α-methylene group.[2-5] We reported the isolation of a single product from the condensation of 2-tetralone with dicyandiamide.[2,4] Although cyclization can theoretically involve the methylene group on either side of the carbonyl group of 2-tetralone, leading to **1** or **2**, we have established the structure of the reaction product as 1,3-diamino-5,6-dihydrobenzo[*f*]quinazoline (**1**).[6,7] A number of substituted 1,3-diamino-5,6-dihydrobenzo[*f*]quinazolines were subsequently prepared by this route.[8,9] Application of this versatile pyrimidine ring-forming reaction to bicyclic aromatic ketones is now described; in connection with the present work, an interesting thermal rearrangement was observed and confirmed by alternative synthesis.

A disproportionation reaction of compound **1** was conducted in the presence of tetralin and 10% palladium–charcoal catalyst in 2-(2-ethoxyethoxy)ethanol at 198–202° for 38 hr. The major product was 2,4-diaminobenzo[*g*]quinazoline (**5a**), the structure of which was proved by comparison with an authentic sample prepared by an unambiguous synthesis.[10-14] Isolation of **5a** suggested that the product of condensation of 2-tetralone and dicyandiamide might have been 2,4-diamino-5,10-dihydrobenzo[*g*]quinazoline. It is now obvious that **5a** resulted by rearrangement under disproportionation conditions. This, to our knowledge, is the only example of a thermal rearrangement of a benzo[*f*]quinazoline to a benzo[*g*]quinazoline. The minor product from this reaction (**10**) retained the benzo[*f*]quinazoline ring structure of the parent compound.[15]



An authentic sample of 2,4-diaminobenzo[*g*]quinazoline was prepared according to the procedures of Curd, Landquist, and Rose[10] and Legrand[11-14] with certain modifications. 2,4-Dihydroxybenzo[*g*]quinazoline (**3a**) was obtained by reaction of 2-amino-3-

(1) This investigation was supported in part by research grant C6516 and research career development award K3-CA-22,151 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) S. K. Sengupta, S. Chatterjee, H. Kangur, and E. J. Modest, Abstracts of Papers, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 3, 1963, p 37-L.

(3) E. J. Modest, G. E. Foley, and S. Farber, *Acta, Unio Int. Contra Cancrum*, **16**, 702 (1960).

(4) E. J. Modest, S. Chatterjee, and H. Kangur, *J. Org. Chem.*, **27**, 2708 (1962).

(5) E. J. Modest, S. Chatterjee, and H. K. Protopapa, *J. Org. Chem.*, **30**, 1837 (1965). This is part III of the series.

(6) A. Rosowsky, E. P. Burrows, S. K. Sengupta, and E. J. Modest, Abstracts of Papers, First International Congress of Heterocyclic Chemistry, Albuquerque, N. M., June 15, 1967, Abstract No. 104.

(7) E. P. Burrows, A. Rosowsky, and E. J. Modest, *J. Org. Chem.*, **32**, 4090 (1967).

(8) A. Rosowsky and E. J. Modest, *Ann. N. Y. Acad. Sci.*, **186**, 258 (1971).

(9) A. Rosowsky, K. K. N. Chen, N. Papathanasopoulos, and E. J. Modest, *J. Heterocycl. Chem.*, in press.

(10) F. H. S. Curd, J. K. Landquist, and F. L. Rose, *J. Chem. Soc.*, 1759 (1948).

(11) A. Etienne and M. Legrand, *C. R. Acad. Sci.*, **229**, 220 (1949).

(12) A. Etienne and M. Legrand, *ibid.*, **231**, 232 (1950).

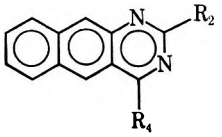
(13) M. Legrand, *ibid.*, **231**, 1318 (1950).

(14) M. Legrand, private communication.

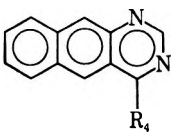
(15) Compound **10** was identified as 3-amino-1-[2-(2-ethoxyethoxy)-ethoxy]benzo[*f*]quinazoline (see Experimental Section). Mass spectrometric analysis of **10**, together with the fragmentation pattern of the ether side chain, is described separately: S. K. Sengupta, H. K. Protopapa, E. J. Modest, and B. C. Das, *Org. Mass Spectrom.*, (submitted for publication).

naphthoic acid and urea.[10,16] Chlorination of **3a** with phosphorus oxychloride in refluxing bromobenzene afforded 2,4-dichlorobenzo[*g*]quinazoline (**4a**); conventional chlorination in refluxing phosphorus oxychloride was less satisfactory. The method of Legrand[13,14] for amination of **4a** to **5a** in ethanolic ammonia required increased temperature, pressure, and reaction time for complete reaction.

In view of the isolation of **5a** from the disproportionation reaction, several additional derivatives of the seldom reported benzo[*g*]quinazoline ring system were synthesized for possible comparative purposes in connection with the solid-phase dehydrogenation described below. Condensation of formamide with 2-amino-3-naphthoic acid *via* Niementowski's reaction[17] afforded 4-hydroxybenzo[*g*]quinazoline (**3b**), which was converted into 4-chlorobenzo[*g*]quinazoline (**4b**). Amination of **4b** gave **5b**.[13,18] This amination was more facile than that of 2,4-dichlorobenzo[*g*]quinazoline (**4a**).



3a, $R_2 = R_4 = OH$
4a, $R_2 = R_4 = Cl$
5a, $R_2 = R_4 = NH_2$
6, $R_2 = NH_2$; $R_4 = OH$



3b, $R_4 = OH$
4b, $R_4 = Cl$
5b, $R_4 = NH_2$

2-Amino-4-hydroxybenzo[*g*]quinazoline (**6**) was synthesized in low yield by high-temperature condensation of 2-amino-3-naphthoic acid and guanidine in boiling phenol. The same material (**6**) was obtained in good yield when **5a** was subjected to selective acid hydrolysis of the 4-amino group. The preferential hydrolysis of the 4- and 6-amino groups as compared with the 2-amino groups in pyrimidine ring systems is well known.[19]

When the dehydrogenation of **1** was carried out with 10% palladium–charcoal catalyst at 270–320° without solvent, a reaction product was obtained which was shown to be a mixture of three components by paper chromatography. One component, the starting material (**1**), was removed by sublimation. Sublimation of the residue at a higher temperature yielded a mixture of the other two components. Fractional crystallization from absolute ethanol yielded the second component in pure form, identified as 3-aminobenzo[*f*]quinazoline (**7**) by comparison with an authentic sample.[20,21] Obviously deamination had occurred during or following dehydrogenation of **1** with the formation of 3-aminobenzo[*f*]quinazoline (**7**) as one product of the reaction. Dehydrogenation had been accompanied by evolution of considerable gaseous ammonia. Primary aromatic amino groups can be hydrogenolyzed in the presence of various catalysts.[22]

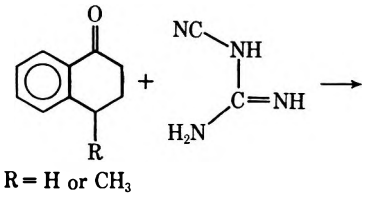
(16) M. T. Bogert and G. Scatchard, *J. Amer. Chem. Soc.*, **41**, 2052 (1919).
(17) S. v. Niementowski, *J. Prakt. Chem.*, [2] **51**, 564 (1895).
(18) A. R. Osborn, K. Schofield, and L. N. Short, *J. Chem. Soc.*, 4191 (1956).
(19) (a) E. C. Taylor and C. K. Cain, *J. Amer. Chem. Soc.*, **71**, 2282 (1949); (b) R. B. Trattner, G. B. Elion, G. H. Hitchings, and D. M. Sharefkin, *J. Org. Chem.*, **29**, 2674 (1964).
(20) A. Rosowsky, N. Papathanasopoulos, M. E. Nadel, S. K. Sengupta, and E. J. Modest, Abstracts of Papers, 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 28, 1966, I-1.
(21) A. Rosowsky and E. J. Modest, *J. Org. Chem.*, **31**, 2607 (1966).
(22) Nathan Kornblum in "Organic Reactions," Vol. II, Wiley, New York, N. Y., 1947, p 262.

Neither fractional crystallization nor cellulose column chromatography afforded a pure sample of the third component. Therefore, the original dehydrogenation mixture was subjected to ion exchange chromatography with a cation exchange resin, and the column was eluted with different strengths of aqueous hydrochloric acid. Hydrochloric acid (2 *N*) extracted monoamine **7**, identified as the free base. The 4 *N* hydrochloric acid eluate was free from **7**. Work-up afforded a single, pure compound with infrared absorption at 5.85 μ; it was shown to be an amido compound by elemental analysis. The material, isomeric with **6**, was identified as 1-hydroxy-3-aminobenzo[*f*]quinazoline (**8**) by comparison with an authentic sample.[20,21] This must have come from 1,3-diaminobenzo[*f*]quinazoline (*via* solvent-free dehydrogenation of **1**) by acid hydrolysis during the prolonged process of elution from the column. The preferential acid hydrolysis of the 1-amino group of 1,3-diaminobenzo[*f*]quinazoline has already been recorded,[21] as well as the formation of 1,3-diaminobenzo[*f*]quinazoline by mild, selenium dioxide–acetic acid dehydrogenation of **1**.[6,7]

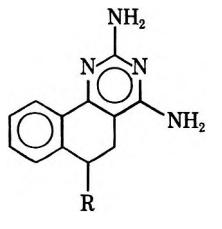
Mild nitrosation of **1** yielded 1-hydroxy-3-amino-5,6-dihydrobenzo[*f*]quinazoline (**9**) by preferential reaction of the 1-amino group. Dehydrogenation of **9** gave **8**. Nitrosation of **1** under forcing conditions gave small amounts of 1,3-dihydroxybenzo[*f*]quinazoline.

In summary of the palladium–charcoal reactions on **1**, dehydrogenation under disproportionation conditions with tetralin in 2-(2-ethoxyethoxy)ethanol gave the rearranged product **5a** in major yield, whereas dehydrogenation without solvent afforded the unrearranged **7** and **8**, derivable from **1** by dehydrogenation and by deamination and hydrolysis, respectively, of the 1-amino group. Since each reaction was repeated several times and since the purity of **1** was rigorously substantiated (see Experimental Section), it is clear that the disproportionation reaction involves extensive ring rearrangement, for which we cannot at present offer a mechanistic explanation. See Scheme I.

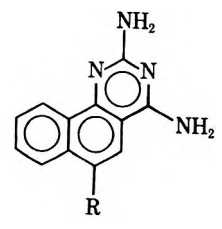
Studies were also carried out with 1-tetralone and related bicyclic ketones. Reaction of 1-tetralone with dicyandiamide afforded 2,4-diamino-5,6-dihydrobenzo[*h*]quinazoline (**11a**) in about 58% yield. Similarly, 2,4-diamino-5,6-dihydro-6-methylbenzo[*h*]quinazoline (**11b**) was prepared from 4-methyl-1-tetralone in 63% yield. In contrast to **1** (the 2-tetralone condensation product), **11a** was readily dehydrogenated to the fully



R = H or CH_3



11a, R = H
b, R = CH_3



12, R = H
(from **11a**)

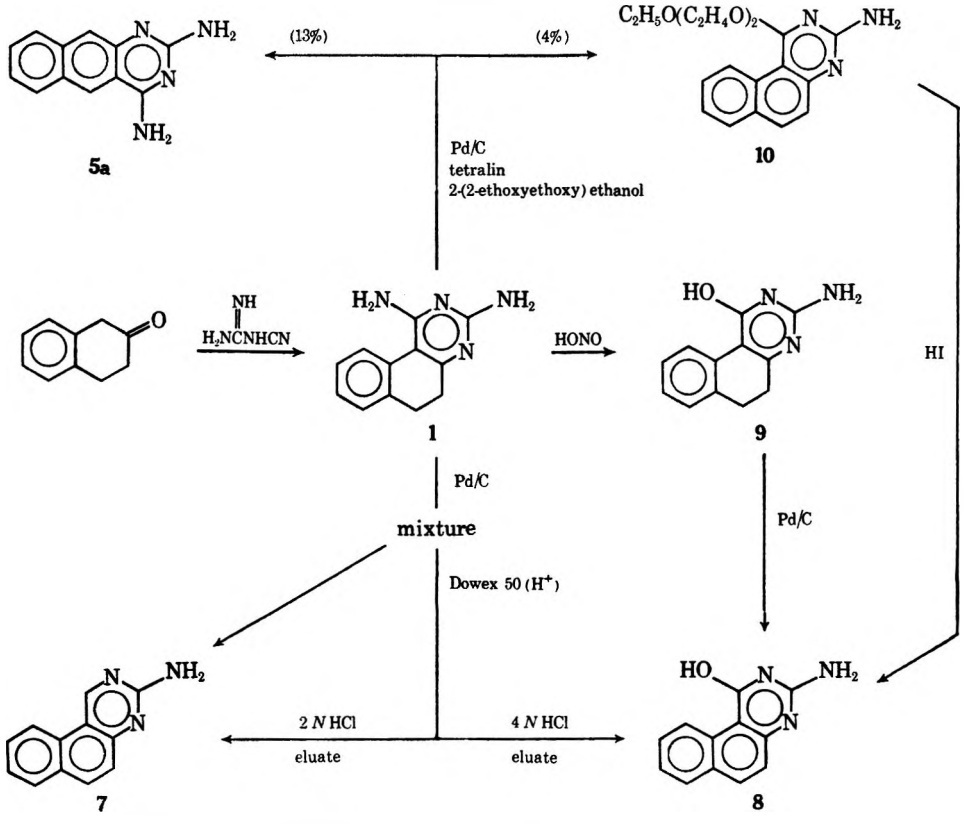
Table I

Nmr[a] and Ultraviolet Spectra

Compd	δ, ppm: Methylene	Aromatic	(Solvent)	λmax, nm (ε × 10⁻³): EtOH	pH 1	DMF
1	3.03 (singlet)	7.63 (four peaks)	(TFA)	276 (18.7)	271 (17.1)	282 (14.9)
				294 (16.9)	282 (13.1)[b]	305 (16.9)
	2.85 (multiplet)	7.63 (multiplet)	(DMF-d_7)		289 (12.1)[b]	
9	3.01 (singlet)	7.40 (four peaks)	(TFA)	235 (10.0)	262 (18.6)	267 (8.3)
				264 (19.3)	305 (9.1)	297 (8.4)
	2.75 (multiplet)	7.92 (quartet)	(DMF-d_7)	284 (7.1)		328 (15.5)
				296 (7.9)		
		7.15 (triplet)	(DMF-d_7)	325 (12.2)		
11a	3.05 (octet)	7.75 (multiplet)	(TFA)	240 (25.5)	226 (17.0)	281 (3.3)
				280 (3.2)[b]	239 (16.9)	292 (2.9)
				292 (3.3)	286 (5.9)[b]	332 (7.1)
	2.85 (multiplet)	7.63 (multiplet)	(DMF-d_7)	328 (8.35)	298 (8.6)	
					320 (12.7)[b]	
					327 (13.4)	
					340 (9.0)[b]	
13	3.23 (octet)	7.35 (singlet)	(TFA)	243 (17.2)	240 (25.5)	
				264 (14.1)	333 (13.1)	
				269 (13.3)	347 (8.9)[b]	
				299 (7.6)		
				330 (2.6)[b]		
15	4.10 (singlet)	8.05 (three peaks)	(TFA)	238 (25.5)	226 (17.8)	283 (3.2)
				284 (4.5)	238 (16.5)	291 (3.8)
				291 (6.1)	316 (18.6)	322 (6.13)
				318 (10.4)	329 (12.9)	

[a] Nmr peak values are center of multiple peaks wherever applicable. [b] Shoulder.

Scheme I

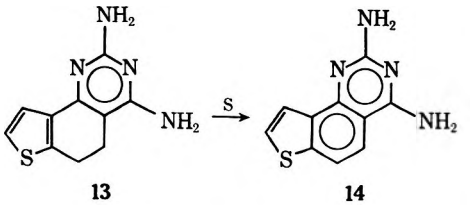


aromatic derivative 2,4-diaminobenzo[*h*]quinazoline (**12**) with 10% palladium–charcoal or sulfur.

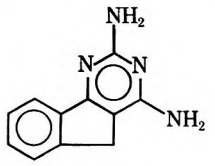
A thiophene analog of 1-tetralone, 4-keto-4,5,6,7-tetrahydrothionaphthene, reacted with dicyandiamide with formation of the expected 2,4-diaminopyrimidine derivative **13** in good yield; **13** underwent smooth dehydrogenation with sulfur to **14** in 70% yield. Compounds **13** and **14** represent the 2,4-diaminothieno-[2,3-*h*]quinazoline ring system, which, to the best of our knowledge, has not been reported in the literature.

Condensation of 1-indanone with dicyandiamide gave 2,4-diamino-5*H*-indeno[1,2-*d*]pyrimidine (**15**) (78% yield).

Compounds **11a** and **15**, which may be considered



13 14



15

tricyclic analogs of 2,4-diamino-6-phenylpyrimidine, have multiple ultraviolet absorption peaks in ethanol, whereas 2,4-diamino-6-phenylpyrimidine itself shows only two absorption maxima in ethanol, at 240 and 305 nm.[23] In contrast, the ultraviolet absorption spectrum of **1** in ethanol is very similar to that of the analogous 2,4-diamino-5-phenylpyrimidine,[23] having only two maxima. A reasonable explanation for these observations is that steric interaction between the 1-amino group and the proton at C-10 of **1** may effect enough loss of planarity to interrupt conjugation of the aromatic rings and to produce a loss of fine structure in the ultraviolet spectrum.[24] Replacement of the 1-amino group in **1** by a 1-oxo (or hydroxy) function in **9** restores planarity (multiple absorption maxima) (Table I).

The nmr spectrum of **1** in trifluoroacetic acid shows a singlet methylene peak (Table I), but the spectrum of **11a** shows a methylene octet in that solvent. Methylene multiplets are observed for both compounds in dimethylformamide-d_7, although the characteristic splitting pattern of the methylene protons of **1** differs from that of **11a**. Thus, the nmr data support the conclusion from the ultraviolet data that **11a** is a relatively planar, conjugated molecule in contrast to **1**.

Experimental Section[27]

1,3-Diamino-5,6-dihydrobenzo[*g*]quinazoline (1).—A mixture of 3.4 g (0.040 mol) of dicyandiamide and 3.6 g (0.025 mol) of 2-tetralone was heated for 1 hr (partial solution) at 150–170° (internal temperature) and then at 180–185° for another 45 min (complete solution). The heating was continued for 1 hr at 190°, at which point water started evolving and a yellow solid started separating from the reaction mixture. The resulting solid was washed with acetone and crystallized directly from dimethylformamide as a colorless, microcrystalline solid, yield 2.6 g (50%), mp 268–270°. Several further crystallizations from dimethylformamide afforded analytically pure material, yield 2 g (38%), mp 263–264°, R_{Ad} 1.41 (solvent A), 1.69 (solvent B), 1.63 (solvent C).

Anal. Calcd for $C_{12}H_{12}N_4$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.93; H, 5.93; N, 26.49.

Formation of 5a by Disproportionation of 1.—This procedure was the best of a number of experiments and was run three times. The purity of the starting material, 1,3-diamino-5,6-dihydrobenzo[*f*]quinazoline (1), was carefully established by comparison (paper chromatography, ultraviolet and nmr spectra, mixture melting point) with an authentic sample of the isomeric 2,4-diamino-5,10-dihydrobenzo[*g*]quinazoline, synthesized from methyl 2-tetralone-3-carboxylate.[28] Insofar as possible, all of the following operations, including the crystallizations, were carried out under a nitrogen atmosphere. A mixture of pure **1** (1.0 g, 0.0047 mol) and 10% palladium–charcoal (0.5 g) in tetralin (20 ml) and 2-(2-ethoxyethoxy)ethanol (45 ml) was refluxed for 38 hr in a flask equipped with magnetic stirring and an immersion thermometer. The internal temperature was maintained at 198–202°. The progress of the reaction was followed spectrophotometrically by the appearance of $\lambda_{max}^{pH\ 1}$ 248, 307, 321, and 374 nm. The reaction mixture was filtered while hot and the palladium–charcoal residue was washed with a hot 2:1 mixture of benzene and 2-(2-ethoxyethoxy)ethanol (300 ml). The combined reaction filtrate and washings (yellow fluorescent solution) were reduced to one-third volume. The remaining solvent was removed initially by vacuum distillation at 84–86° (internal temperature) and finally by prolonged evaporative distillation at 75–140° (0.5–0.7 mm). The colorless distillate (1.4 g) deposited some unchanged starting material (**1**, 0.25 g) upon prolonged refrigeration. Sublimation of the distillation residue at 180–190° (0.5–0.7 mm) for 24 hr yielded two distinct bands of sublimate: a more volatile, nearly colorless fraction (A), and a less volatile, yellow crystalline fraction (B). Sublimate B was dissolved in a 1:1 mixture of hot benzene and absolute ethanol (25 ml) and filtered free of a small insoluble residue. The volume of the yellow fluorescent filtrate was reduced to 2–3 ml. Overnight refrigeration afforded yellow needles (**5a**), yield 99.1 mg (13.2% based on recovered starting material), mp 284–285°. Two further crystallizations of this solid from absolute ethanol afforded analytically pure, yellow needles, yield 50.9 mg (6.8%), mp 284–285°, dried for analysis for 23 hr at 30–50° *in vacuo*.

Anal. Calcd for $C_{12}H_{10}N_4$: C, 68.55; H, 4.80; N, 26.65. Found: C, 68.49; H, 4.94; N, 26.44.

A mixture melting point of this material with an authentic sample of **5a** prepared by a synthetic route was undepressed (mp 284–286°) and the two samples had identical ultraviolet and infared absorption spectra and R_{Ad} values: R_{Ad} 1.29 (solvent A), 1.17 (solvent B), 1.23 (solvent C).

Fractional crystallization of sublimate A from absolute ethanol afforded 49 mg (4.2%) of colorless solid, recrystallization of which from ethanol gave analytically pure **10** as colorless needles, mp 116–118°, molecular formula $C_{18}H_{21}N_3O_3$ (M^+ 327 amu). Ether cleavage of **10** with hydriodic acid generated **8**. These data, together with the mass spectrometric fragmentation behavior of the side chain, confirmed the identity of **10** in sublimate A.[15]

2,4-Dihydroxybenzo[*g*]quinazoline (3a).—A mixture of 2-amino-3-naphthoic acid (12 g, 0.064 mol), urea (24 g, 0.4 mol), and solid phenol (60 g) was fused at 180–190° (bath temperature) for 15 min and then heated under stirring and gentle reflux (air condenser) for 90 min, after which the resulting melt was cooled to *ca.* 70° and absolute ethanol (60 ml) was added cautiously with stirring. The solid residue was collected and dried, yield 12 g (90%), mp 345–350°, and crystallized (Darco[29]) from glacial acetic acid as a colorless solid, yield 10.15 g (77%), mp >360°

(23) (a) P. B. Russell, *J. Chem. Soc.*, 2951 (1954); (b) B. Roth and J. Z. Strelitz, *J. Org. Chem.*, **34**, 821 (1969).

(24) By analogy, the ethanolic spectrum of the sterically hindered 9,10-dihydro-4,5-dimethylphenanthrene has only one maximum, at 260 nm, similar to the spectrum of biphenyl, but unlike the spectrum of the relatively planar 9,10-dihydrophenanthrene, which has three maxima up to 330 nm.[25,26]

(25) (a) G. H. Beavan, D. M. Hall, M. S. Lesslie, and E. E. Turner, *J. Chem. Soc.*, 854 (1952); (b) K. Mislow, M. A. W. Glass, H. B. Hopps, E. Simon, and G. H. Wahl, Jr., *J. Amer. Chem. Soc.*, **86**, 1710 (1964).

(26) H. Suzuki, *Bull. Chem. Soc. Jap.*, **35**, 1715 (1962).

(27) The infrared spectra were recorded on a Perkin-Elmer Model 137B recording spectrophotometer in potassium bromide or potassium chloride disks. Uv spectra were measured with Cary Model 11 and Model 15 spectrophotometers at pH 1 (ethanolic 0.1 *N* hydrochloric acid), ethanol, and dimethylformamide. The nmr spectra were determined on a Varian Associates Model A-60 recording spectrophotometer in trifluoroacetic acid and heptadeuteriodimethylformamide. Tetramethylsilane (TMS) was used as the internal standard and all signals are given in parts per million (δ) relative to TMS at δ 0. Ascending paper chromatography was done on Whatman No. 1 paper in the following solvent systems: A, *n*-butyl alcohol–acetic acid–water (4:1:1); B, *n*-butyl alcohol saturated with water; C, isopropyl alcohol–ammonium hydroxide–water (70:5:25). Adenine was used as an internal standard in all chromatograms; spot locations are expressed as R_{Ad} values with adenine at 1.00. All melting points were measured in Pyrex capillary tubes in a modified Wagner–Meyer apparatus [E. C. Wagner and J. F. Meyer, *Ind. Eng. Chem., Anal. Ed.*, **10**, 584 (1938)] at a heating rate of 2°/min and are corrected wherever possible. Microanalyses were performed by the Scandinavian Microanalytical Laboratories, Herlev, Denmark, and Galbraith Laboratories, Knoxville, Tenn.

(28) A. Rosowsky, P. C. Huang, and E. J. Modest, Abstracts of Papers, Second Northeast Regional Meeting of the American Chemical Society, Providence, R. I., Oct 20, 1970, p 83.

(29) Darco G-60 activated carbon, Atlas Chemical Industries, Inc., Wilmington, Del.

(lit.[10,16] mp 358–359° and 360°). For analysis the material was recrystallized several times from glacial acetic acid.

Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.65; H, 3.71; N, 13.18.

2,4-Dichlorobenzo[*g*]quinazoline (4a).—A mixture of **3a** (3.0 g, 0.014 mol), bromobenzene (150 ml, bp 151–152°), and phosphorus oxychloride (30 ml) was refluxed for 3 hr. Another 30-ml portion of phosphorus oxychloride was added and reflux was continued for another 12 hr. After removal of volatile solvents under reduced pressure, the residue was poured onto ice and brought to pH 10 with 1 *N* sodium carbonate. The aqueous phase was then stirred for 15 min with the addition of chloroform (150 ml) and thoroughly extracted with additional chloroform. The combined chloroform extracts were washed with water and dried. Removal of solvent gave a yellow residue (3 g, 90%), mp 200–204°. This material was sublimed at 160–165° (0.5 mm) and a lemon-yellow sublimate, yield 2.4 g (66%), mp 203–204°, was obtained and crystallized from dry benzene as yellow needles, yield 2.23 g (70%), mp 205–206° (lit.[13] mp 205°). For analysis this material was crystallized twice from benzene and dried at 60° (0.5 mm) for 10 hr. (The material had a tendency to sublime even at low temperatures.)

Anal. Calcd for $C_{12}H_6N_2Cl_2$: C, 57.86; H, 2.43; Cl, 28.47; N, 11.25. Found: C, 57.99; H, 2.57; Cl, 28.11; N, 11.05.

2,4-Diaminobenzo[*g*]quinazoline (5a) from 4a.—A mixture of **4a** (300 mg, 0.0012 mol) and dry ethanol (60 ml) saturated with gaseous ammonia at 0° was heated at 170–180° for 70 hr in a stainless steel reactor. A nitrogen atmosphere was maintained during all subsequent operations, including the crystallizations. The greenish-yellow reaction mixture was taken to dryness on a steam bath with the aid of a jet of nitrogen. After extraction with 5% aqueous sodium hydroxide solution (20 ml) on a steam bath for 15 min, the greenish-yellow solid was collected, washed, dried (200 mg, 80%), and crystallized from absolute ethanol by concentration of the solution with a jet of nitrogen as yellow-green needles, yield 175 mg (70%), mp 280–282°, negative Beilstein test. Several crystallizations from absolute ethanol afforded yellow-green needles: yield 65 mg (25%); mp 284–286° (lit.[13,14] mp 285°, 287°); R_{Ad} 1.33 (solvent A), 1.14 (solvent B), 1.23 (solvent C).

Anal. Calcd for $C_{12}H_{10}N_4$: C, 68.55; H, 4.80; N, 26.65. Found: C, 68.34; H, 4.96; N, 26.59.

2-Amino-4-hydroxybenzo[*g*]quinazoline (6). A. From 2-Amino-3-naphthoic Acid.—A mixture of guanidine carbonate (24 g, 0.13 mol) and solid phenol (40 g) was fused at 180–190° (bath temperature) for 15 min and then 2-amino-3-naphthoic acid (24 g, 0.064 mol) was added. The mixture was heated under gentle reflux (air condenser) with stirring for 5 hr. After trituration of the reaction mixture with ethanol (60 ml), the resulting solid material was extracted with refluxing glacial acetic acid (350 ml). Crystallization of the insoluble residue from 8 *N* hydrochloric acid yielded 6 HCl (4 g, 25%), no melting point below 320°. The hydrochloride (500 mg) was stirred with 10 ml of concentrated ammonium hydroxide for 1 hr at room temperature and the resultant yellow solid material (6) (300 mg) was crystallized from dimethylformamide: yield 100 mg; mp >330°; R_{Ad} 1.46 (solvent A), 1.45 (solvent B), 1.18 (solvent C).

Anal. Calcd for $C_{12}H_9N_3O$: C, 68.24; H, 4.30; N, 19.89. Found: C, 68.05; H, 4.89; N, 19.87.

B. By Acid Hydrolysis of 5a.—A solution of 2,4-diaminobenzo[*g*]quinazoline (**5a**, 100 mg, 0.48 mmol) in 6 *N* hydrochloric acid (25 ml) was heated under reflux for 1 hr. The yellow reaction mixture started depositing white needles after 0.5 hr and the color of the solution was gradually discharged. The crystals were collected and dried, yield 100 mg (90%), no melting point below 350°. This material was stirred with concentrated ammonium hydroxide (10 ml) for 5 min, collected, washed with warm water, and dried as a bright yellow solid, yield 90 mg (80%), no melting point below 350°, identical with **6** prepared by procedure A.

4-Hydroxybenzo[*g*]quinazoline (3b).—A mixture of 2-amino-3-naphthoic acid (5 g, 0.027 mol) and formamide (2.5 g, 0.056 mol) was fused at 150–155° (internal temperature) in a beaker for 10 min with constant hand stirring to prevent formation of any lumps in the melt. Another portion of formamide (2.0 g, 0.44 mol) was added and the heating at 150–155° was continued for 4 hr with occasional stirring to keep the mass in a thin, pasty form. The reaction mixture was stirred with cold water (50 ml) and the slurry was filtered. Several crystallizations of the residue (4.6 g, 83%) from glacial acetic acid, the first with Darco, afforded colorless needles, mp 279–280° (lit.[11] mp 278°).

Anal. Calcd for $C_{12}H_8N_2O$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.21; H, 4.42; N, 14.15.

4-Chlorobenzo[*g*]quinazoline (4b).—A fine suspension of **3b** (4 g, 2.04 mmol) in 200 ml of chlorobenzene was refluxed for 34 hr with 25 ml of freshly distilled phosphorus oxychloride. The red solution was cooled, filtered through a sintered glass funnel, and poured into an aqueous suspension (400 ml) of sodium carbonate (30 g) and calcium hydroxide (30 g) containing crushed ice. After 30 min of stirring, the chlorobenzene layer was separated and the aqueous alkaline layer (pH 8) was extracted three times with chloroform. The combined organic extracts were washed with water (10 ml) and dried. The solvents were removed and the residue, yield 2.8 g (68%), mp 176–178°, was sublimed at 180–190° (0.5–0.7 mm), yield 1.9 g (45%) of yellow sublimate, mp 177–179° (lit.[11] mp 179°). Several crystallizations from benzene yielded analytically pure yellow needles, mp 178–179°, in 40% overall recovery, R_{Ad} 1.86 (solvent A), 1.70 (solvent C).

Anal. Calcd for $C_{12}H_7N_2Cl$: C, 67.14; H, 3.29; Cl, 16.52; N, 13.05. Found: C, 67.55; H, 3.36; Cl, 16.56; N, 12.97.

4-Aminobenzo[*g*]quinazoline (5b).—Amination of **4b** (400 mg, 1.9 mmol) by a procedure similar to that employed in the amination of **4a** (except that a nitrogen atmosphere was not necessary) afforded 300 mg of crude **5b**, mp 324–331°, which was halogen-free. Sublimation at 140–180° (0.5 mm) gave a yellow sublimate, yield 180 mg (50%), mp 335–338°. Three crystallizations from absolute ethanol yielded yellow needles, 120 mg (34% overall yield), mp 337–338° (lit. mp 363°,[11,12] *ca.* 365° dec[18]).

Anal. Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.62; H, 4.64; N, 21.61.

Isolation of 3-Aminobenzo[*f*]quinazoline (7) and 1-Hydroxy-3-aminobenzo[*f*]quinazoline Hydrochloride (8 HCl) on Dehydrogenation of 1.—An intimate mixture of **1** (800 mg) and 10% palladium–charcoal (70 mg) was placed in a Heymann's apparatus and heated in a metal bath at 270–300° under a slow stream of nitrogen. The evolved gases were found to contain ammonia throughout the reaction period of 1 hr. The yellow sublimate that had deposited on the cold finger was collected and the residue containing the catalyst was extracted with dimethylformamide. The total solid material obtained (430 mg, 53%) was sublimed at 120–150° (0.5 mm) and the sublimate, on crystallization from absolute ethanol, yielded **1** (100 mg), mp 260–262°, $\lambda_{max}^{pH\ 1}$ 272 nm. The residue in the sublimation tube on further sublimation at 170–180° (0.5 mm) furnished a yellow solid (180 mg, 23%), mp 201–205°.

The latter sublimate (170 mg) was dissolved in 150 ml of warm 0.5 *N* hydrochloric acid and chromatographed on a column of Dowex 50W-X8 (H^+) cation exchange resin, 100–120 mesh (column volume 6.5 ml in a 50-ml buret). Elution with 2 *N* hydrochloric acid (the progress of the elution being monitored by the absorbance of the characteristic 291-nm peak) gave 30 mg of white solid which on treatment with dilute (1:3) aqueous ammonia (30 ml) at room temperature furnished a yellow solid (15 mg). Crystallization from absolute ethanol gave yellow solid (12 mg), mp 263–264° dec, R_{Ad} 1.80 (solvent A), 1.81 (solvent B), 1.72 (solvent C). A mixture melting point of this sample with authentic **7** prepared in this laboratory was undepressed.[20,21]

Anal. Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.53. Found: C, 73.54; H, 4.61; N, 21.59.

Further elution with 4 *N* hydrochloric acid afforded colorless material (60 mg, λ_{max}^{KBr} 5.85 μ), which was redissolved in warm 4 *N* HCl, filtered, and refrigerated. Colorless needles of **8** HCl were collected, yield 35 mg, no melting point below 360°, R_{Ad} 1.78 (solvent B), 1.43 (solvent C). (The mother liquor afforded another 15 mg of product on evaporation.)

Anal. Calcd for $C_{12}H_9N_3O \cdot HCl$: C, 58.19; H, 4.07; Cl, 14.32; N, 16.96. Found: C, 58.58; H, 4.21; Cl, 13.87; N, 16.60.

The free base of **8** from this analytical sample was identical with free base from authentic $8 \cdot {}^1/_2CH_3COOH$ prepared previously.[21]

3-Amino-1-hydroxy-5,6-dihydrobenzo[f]quinazoline (9.)—Sodium nitrite (500 mg, 7.2 mmol) in water (2 ml) was added dropwise at 5–10° to a stirred solution of 1,3-diamino-5,6-dihydrobenzo[*f*]quinazoline (**1**, 500 mg, 2.35 mmol) in 4 *N* hydrochloric acid (80 ml). The reaction mixture was stirred for an addi-

tional 0.5 hr at 5–10° and then at room temperature for 16 hr. The white solid that separated was collected and combined with additional material obtained on concentration of the filtrate to *ca.* 10 ml. The combined solids were stirred with 4 *N* ammonium hydroxide for 30 min. A greyish-white solid was obtained: yield 300 mg (60%); no melting point below 330°; λ_{max}^{KBr} 6.0 and 6.1 μ. Several crystallizations from 25% acetic acid yielded 100 mg (20%) of off-white solid, no melting point below 340°, R_{Ad} 1.79 (solvent A), 1.77 (solvent B), 1.46 (solvent C).

Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.38; H, 5.25; N, 19.79.

1,3-Dihydroxy-5,6-dihydrobenzo[*f*]quinazoline.[30]—The preceding nitrosation of 1 was carried out under forcing conditions (with twice the ratio of nitrous acid and at 40–50° for 5 hr) and the reaction product was triturated with hot water and crystallized successively from 25% acetic acid and 95% ethanol (Darco). In addition to **9**, another compound was isolated as off-white crystals: yield 60 mg; mp 342–345°; λ_{max}^{EtOH} 303 nm (ϵ 9150), 253 (15,400); λ_{inf}^{EtOH} 294 nm; λ_{max}^{KBr} 5.78, 6.1 μ.

Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.27; H, 4.70; N, 13.08. Found: C, 67.12; H, 4.86; N, 13.15.

3-Amino-1-hydroxybenzo[*f*]quinazoline Hydrochlorides (8 HCl).—A mixture of 3-amino-1-hydroxy-5,6-dihydrobenzo[*f*]-quinazoline (**9**, 90 mg, 0.39 mmol) and 5% palladium–charcoal (30 mg) was heated slowly in a Heymann's apparatus (nitrogen flow) from 210 to 320° and then kept for 1.5 hr at 300–320°. The sublimate on the cold finger (20 mg, 22%) was purified twice by dissolution in 2 *N* hydrochloric acid and precipitation with ammonia. Crystallization from 9 *N* hydrochloric acid yielded white needles of **8** HCl: yield 10–11 mg (10%); no melting point below 360°; R_{Ad} 1.70 (solvent A), 1.78 (solvent B), 1.43 (solvent C). The material was identical with the sample of **8** HCl obtained by solid state dehydrogenation of **1**.

2,4-Diamino-5,6-dihydrobenzo[*h*]quinazoline (11a).—A mixture of 1-tetralone (1.46 g, 0.01 mol), dicyandiamide (1.26 g, 0.015 mol), and Triton B (0.1 ml, as catalyst) was heated for 5.5 hr at 195–201° (internal temperature). A clear solution resulted in 25 min and solid started to deposit shortly thereafter. The yellowish semisolid mixture was evaporated to dryness. Trituration with 4 ml of 3 *N* hydrochloric acid yielded solid, 2.31 g (55%). Crystallization from 1 *N* hydrochloric acid (Darco) gave colorless needles (46% recovery), which darken and shrink somewhat above 245° but do not melt below 310°. Recrystallization from 50% ethanol afforded analytically pure colorless needles, no melting point below 310°.

Anal. Calcd for $C_{12}H_{12}N_4 \cdot HCl \cdot H_2O$: C, 54.03; H, 5.67; Cl, 13.29; N, 21.01. Found: C, 53.90; H, 5.69; Cl, 13.41; N, 21.12.

Basification of an aqueous solution of **11a** HCl with sodium hydroxide gave **11a** (58% yield). Crystallization from 50% ethanol (Darco) yielded analytically pure colorless plates mp 207–209°.

Anal. Calcd for $C_{12}H_{12}N_4$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.74; H, 5.75; N, 26.36.

2,4-Diaminobenzo[*h*]quinazoline (12). A.—An intimate mixture of 2,4-diamino-5,6-dihydrobenzo[*h*]quinazoline (**11a**, 1.0 g, 47 mmol) and sulfur (0.23 g, 71 g-atoms) was heated for 0.5 hr in an open test tube at 210–280° (bath temperature). The dark brown, glassy melt was pulverized and purified by high vacuum sublimation at 200–220° (0.005–0.001 mm) as a yellow crystalline sublimate, yield 0.25 g (25%), mp 262–275°. One more sublimation afforded analytically pure yellow prisms, mp 273–277°.

Anal. Calcd for $C_{12}H_{10}N_4$: C, 68.55; H, 4.80; N, 26.65. Found: C, 68.52; H, 4.64; N, 26.30.

B.—An intimate mixture of **11a** (0.5 g, 2.3 mmol) and 10% palladium–charcoal (800 mg) was introduced into a metal bath at 200°, slowly heated to 265°, and then maintained at 265–285° for 35 min. A dimethyl sulfoxide extract of the reaction mixture was filtered, concentrated on a steam bath, and triturated with a 1:1 mixture of ether–benzene. The residue (210 mg, 43%) was sublimed twice at 250–260° (0.5–0.7 mm). A yellow solid, yield 30 mg (6%), mp 275–277°, was obtained, identical with the sample of **12** prepared by method A.

2,4-Diamino-6-methyl-5,6-dihydrobenzo[*h*]quinazoline (11b).—A mixture of 4-methyl-1-tetralone (1.60 g, 0.01 mol), dicyandiamide (1.26 g, 0.015 mol), and Triton B (0.08 ml) was heated for 5 hr under nitrogen at 194–204° (internal temperature). A complete solution was not observed at any time. The syrupy reaction mixture was triturated with acetone, yield 0.7 g (31%) of crude tan solid. The mother liquor was evaporated and triturated with ether, yield 1.13 g (15%) of tan crystalline solid. Part of the crude solid, 1.1 g, was dissolved in 80 ml of 95% ethanol (Darco) and the volume of the yellow filtrate was reduced to 4–5 ml. After overnight refrigeration the solid was collected as yellowish rods (0.69 g, 63% recovery), mp 217–222°. Two more crystallizations from 95% ethanol afforded analytically pure, pale yellow plates, mp 223–227°.

Anal. Calcd for $C_{13}H_{14}N_4$: C, 69.00; H, 6.24; N, 24.76. Found: C, 68.77; H, 6.51; N, 24.48.

2,4-Diamino-5,6-dihydrothieno[2,3-*h*]quinazoline (13).—A mixture of 4-keto-4,5,6,7-tetrahydrothianaphthene (9.12 g, 0.06 mol) and dicyandiamide (7.56 g, 0.09 mol) was heated for 5 hr at 182–200° (internal temperature). The reaction mixture was triturated with acetone to obtain yellow crystals (5.41 g). The mother liquor, on evaporation and trituration with ether, yielded 7.7 g of yellow crystalline solid. Crystallization from 95% ethanol (Darco) afforded 6.97 g (63% yield) of off-white crystals. Recrystallization once more from 95% ethanol (recovery 59%) and finally from 50% aqueous ethanol gave the analytical sample, mp 240–246°.

Anal. Calcd for $C_{10}H_{10}N_4S$: C, 55.02; H, 4.62; N, 25.67; S, 14.69. Found: C, 54.97; H, 4.86; N, 25.56; S, 14.57.

2,4-Diaminothieno[2,3-*h*]quinazoline (14).—An intimate mixture of **13** (328 mg, 15 mmol) and sulfur (73 mg, 22.5 g-atoms) was heated for 0.5 hr at 231–278° (bath temperature). The brown crystalline solid was dissolved in 100 ml of 95% ethanol and filtered, and the volume was reduced to 15 ml. After overnight refrigeration, the yellow prismatic solid (230 mg, 71%) melted at 305–308° dec. Recrystallization from 95% ethanol afforded analytically pure yellow rods, mp 320–322° dec.

Anal. Calcd for $C_{10}H_8N_4S$: C, 55.53; H, 3.73; N, 25.91; S, 14.83. Found: C, 55.33; H, 3.72; N, 26.11; S, 14.87.

2,4-Diaminoindeno[1,2-*d*]pyrimidine (15).—Dicyandiamide (0.84 g, 0.01 mol) and 1-indanone (1.98 g, 0.015 mol) was heated for 6 hr at 173–187° (internal temperature). Trituration of the glassy solid with warm acetone afforded a tan powder (1.3 g, 66%) which was crystallized from methanol as yellow prisms (69% recovery), mp 274–277°. Crystallization from 14 ml of 0.1 *N* hydrochloric acid (78% recovery) and then from water gave analytically pure pale yellow needles of the monohydrochloride, which decompose at 355°.

Anal. Calcd for $C_{11}H_{10}N_4 \cdot HCl$: C, 56.29; H, 4.72; Cl, 15.11; N, 23.87. Found: C, 56.40; H, 4.60; Cl, 15.00; N, 23.50.

Registry No.—**1**, 16061-72-6; **3a**, 33986-99-1; **3b**, 33987-00-7; **4a**, 33987-01-8; **4b**, 33987-02-9; **5a**, 33987-03-0; **5b**, 33987-04-1; **6**, 33987-05-2; **7**, 7066-18-4; **8** HCl, 33987-07-4; **9**, 33987-08-5; **10**, 33987-09-6; **11a**, 33987-10-9; **11a** HCl, 33987-11-0; **11b**, 33987-12-1; **12**, 33987-13-2; **13**, 33987-14-3; **14**, 33987-15-4; **15** HCl, 33987-16-5; 1,3-dihydroxy-5,6-dihydrobenzo-[*f*]quinazoline, 33987-17-6.

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(30) This experiment was performed by Miss S. Karin Tinter.

Pyrolysis of Ketone N,N,N-Trimethylhydrazonium Fluoborates. Evidence for the Genesis of Pyridines[1a,b]

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The preparation of α-methyl ketone N,N,N-trimethylhydrazonium iodides (**3**) and fluoborates (**4**) is described. The pyrolysis of **4** affords predominately 2,6-diarylpyridines (**5**). The mechanism, which resembles the Hantzch synthesis, is proposed for the construction of the pyridine ring with the γ carbon arising from the trimethylamine moiety; this proposed pathway is substantiated by the pyrolytic mass spectral, radiolabeling, and product analysis data.

2,6-Diphenylpyridines[1b,2] and fused-ring pyridines[3] have been prepared by pyrolysis of α-methylenic ketone N,N,N-trimethylhydrazonium fluoborates. The details for syntheses of these quaternary salts and the mechanism for this unusual reaction are the subject of the present paper.

Although there are many synthetic schemes describing the preparation of 2,6-diarylpyridines[4] (**5**), most studies of related reactions have been limited by technical difficulties associated with isolation of the desired isomer or in preparation of the starting materials. The best preparative method of **5** is arylation of the pyridine nucleus with organometallic reagents.[5] An alternative less advantageous route to 2,6-disubstituted pyridines is the *in situ* generation of the pyridine nucleus from aldehydes and/or ketones with a source of ammonia.[4a] Cyclizations of this type are well known, but they often produce complex mixtures with low yields of any single isomer. The present work involves a similar ring construction reaction, except that a single 2,6-disubstituted pyridine nucleus is generated from the pyrolysis of α-methylenic ketone N,N,N-trimethylhydrazonium fluoborates.

The chemistry of these and related quaternary hydrazonium derivatives have been neglected except for some sporadic work which demonstrates the unusual sensitivity of this class of compound toward various reaction conditions. For example, acetophenone N,N,N-trimethylhydrazonium iodide (**3a**) underwent a Neber-type reaction when subjected to protic base,[6] gave 2,4-diphenylpyrrole when treated with methylsulfinyl carbanion or sodium isopropoxide[7] and gave phenyl *n*-hexyl ketone when subjected to *n*-butyllithium in hexane.[8] Pyrolysis of neat **3a** was reported by Smith and Most[6a] to show no change until a deep-seated decomposition took place; no organic compounds were isolated from the tarry residue. Repetition of this pyrolysis (**3a**), in our hands, initially corroborated these gross observations.[2] Substitution of fluoborate for iodide as counterion changed the reaction course drastically; then, 2,6-diarylpyridines were isolated as the principal products.

In the present investigation, the influence of counterions and changes in reaction conditions were studied toward understanding the reaction mechanism.

Results

N,N-Dimethylhydrazones.—Most ketones react directly with anhydrous N,N-dimethylhydrazine to give excellent yields of the corresponding N,N-dimethylhydrazones[9] (Table I). Catalysts other than excess N,N-dimethylhydrazine are unnecessary, although several drops of glacial acetic acid[10] have been shown to facilitate this conversion. In general, minimal difficulties were encountered except for 7-nitro-1-tetralone[3] and 4′-nitroacetophenone,[9a] for which other reaction products were obtained without mineral acid catalysis.

N,N,N-Trimethylhydrazonium Iodides.—The quaternization of ketone N,N-dimethylhydrazones with alcoholic methyl iodide afforded the corresponding N,N,N-trimethylhydrazonium iodides (Table I). The facile preparation of these methiodides has been previously described in detail for aldehydes[11] and ketones.[3,6a,12a] Preparative difficulties experienced herein on attempted quaternization with methyl iodide were encountered when other nitrogen functions were present on or in the aromatic nucleus. 3′- or 4′-Nitroacetophenone N,N-dimethylhydrazone gave only a complex mixture of resinous tars from which the desired quaternary product was not obained. Preparation of 2- and 4-acetylpyridine N,N,N-trimethylhydrazonium iodide gave a mixture of the pyridinium

(1) (a) Some of the preliminary results have been presented earlier: D. L. Fishel and G. R. Newkome, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1966, ORGN-204, and G. R. Newkome, Abstracts, Southeast–Southwest Regional Meeting of the American Chemical Society, New Orleans, La., Dec 1970, ORGN-358. (b) Preliminary communication: G. R. Newkome and D. L. Fishel, *Chem. Commun.*, 916 (1970). (c) Louisiana State University. Submitted to Kent State University by G. R. N. in partial fulfillment for the Ph.D. degree, 1966. (d) Kent State University.

(2) D. L. Fishel and G. R. Newkome, *J. Amer. Chem. Soc.*, **88**, 3654 (1966).

(3) G. R. Newkome and D. L. Fishel, *J. Heterocycl. Chem.*, **4**, 427 (1967).

(4) (a) F. Brody and P. R. Ruby, "Pyridine and Its Derivatives," Part I, pp 99–589; (b) L. E. Tenenbaum, "Pyridine and Its Derivatives," Part II, E. Klingsberg, Ed., Interscience, New York, N. Y., 1961, pp 155–298.

(5) See (a) H. Gilman and J. T. Edward, *Can J. Chem.*, **31**, 457 (1953); (b) C. G. Overberger, J. G. Lombardino, and R. G. Hiskey, *J. Amer. Chem. Soc.*, **79**, 6430 (1957); (c) D. Bryce-Smith and A. C. Skinner, *J. Chem. Soc.*, 577 (1963).

(6) (a) P. A. S. Smith and E. E. Most, Jr., *J. Org. Chem.*, **22**, 358 (1957). (b) Other examples of this transformation have been documented: R. F. Parcell, *Chem. Ind. (London)*, 1396 (1963); D. F. Morrow and M. E. Butler, *J. Heterocycl. Chem.*, **1**, 53 (1964); D. F. Morrow, M. E. Butler, and E. C. Y. Huang, *J. Org. Chem.*, **30**, 579 (1965).

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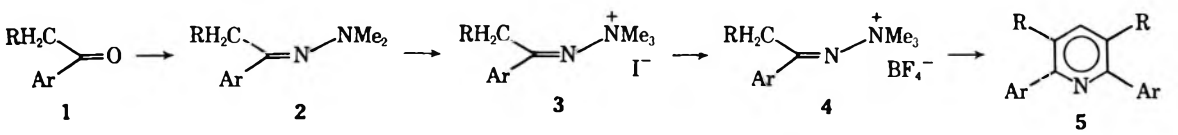
(9) (a) G. R. Newkome and D. L. Fishel, *J. Org. Chem.*, **31**, 677 (1966); (b) *Org. Syn.*, **50**, 102 (1970).

(10) R. H. Wiley and S. H. Chang, *J. Med. Chem.*, **6**, 610 (1963).

(11) R. F. Smith and L. E. Walker, *J. Org. Chem.*, **27**, 4372 (1962).

(12) (a) W. Theilacker and O. R. Leichtle, *Justus Liebigs Ann. Chem.*, **572**, 121 (1951); (b) A. Roe, *Org. React.*, **5**, 193 (1949).

TABLE I[a]



1 2 3 4 5

	Ar	R	Bp, °C (mm)	n_D (°C)	Yield, %	Mp, °C[b]	Yield, %	Mp, °C[b,c]	Yield, %	Mp, °C	Yield, %
a	C_6H_5	H	55–56 (0.15)	1.5443 (26)	92	146–147[d]	87	153–154	96	82–83[e]	55
b	3′-CH_3-C_6H_4	H	*f*			151–152	72	128–130	79	64–65	30
c	4′-$CH_3C_6H_4$	H	*f*			159–160	83	159–160	78	165–166[g]	42
d	4′-FC_6H_4	H	*f*			155–156	90	120–121	87	94–95	*h*
e	4′-ClC_6H_4	H	*f*			145–146	81	146–147	83	155–156	42
f	4′-BrC_6H_4	H	*f*			153–154	72	151–153	75	185–186	39
g	4′-$CH_3OC_6H_4$	H	*f*			152–153	78	146–147	92	197–198	42
h	3′-$NO_2C_6H_4$	H	*f*				0				
i	4′-$NO_2C_6H_4$	H	*f*				0				
j	5-Indanyl	H	*f*			179–180	93	151–152	97	162–163	42
k	2-Naphthyl	H	115–119 (0.10)	1.6324 (20)	90	185–186	67	178–179	92	169–170	21
l	C_6H_5	CH_3	45–46 (0.10)	1.5311 (22)	91	153–156	84	110–111[i]	82	136–137[j]	56
m	C_6H_5	CH_3CH_2	55–56 (0.25)	1.5236 (20)	96	128–130	92	~80[k]	48	146–147	47
n	2-Pyridyl	H	44–45 (0.20)	1.5460 (26)	88	155–156	61	164–165	84		
o	2-(6-Picolyl)	H	53–54 (0.10)	1.5370 (26)	95	168–169	39	172–174	87	164–165	47
p	C_6H_5	C_6H_5	117–118 (0.25)	1.5864 (20)	95	123–124	84	*l*	0		

[a] Satisfactory analytical data (±0.4% for C, H, and N) were reported for all new compounds in this table: Ed. [b] Decomposition points were taken in sealed capillaries. [c] The decomposition points (separated into two layers) were normally 20–30° above the melting points, except where noted. [d] Lit.[6a] mp 145–146° dec. [e] Lit.[28] mp 82°; picrate mp 171° (lit.[29] mp 169°). [f] See ref 9a for the physical data. [g] Picrate mp 176°; M. Scholtz and A. Wiedemann [*Ber.*, **36**, 845 (1903)] reported mp 162° and picrate mp 174°. [h] Yield was not calculated. [i] Decomposition above 150°. [j] Lit.[32] mp 134–135°. [k] Decomposition above 170°. [l] Hydrolysis occurred during preparation.

salt and the diquaternary methiodide; separation was attempted on **3n** only. This difficulty could be easily circumvented by blocking the pyridine nitrogen with a bulky 6-methyl group, thus hindering pyridinium salt formation. Ortho substituted (*e.g.*, 2′,4′-dimethyl-) acetophenones, as well as partially hindered *N,N*-dimethylhydrazones, underwent slow quaternization with refluxing anhydrous methanolic methyl iodide with extended reaction times and usually resulting in lower yields. The use of methyl *p*-toluenesulfonate[11] to quaternize acetophenone *N,N*-dimethylhydrazone gave the desired product.

***N,N,N*-Trimethylhydrazonium Fluoborates.**—Most ketone *N,N,N*-trimethylhydrazonium iodides were easily converted to the corresponding fluoborates (Table I). Preparation of the *N,N,N*-trimethylhydrazonium fluoborates is quite analogous to formation of aromatic diazonium fluoborates as in the Schiemann reaction.[12b] The stable ketone *N,N,N*-trimethylhydrazonium fluoborates (**4**) immediately start to precipitate from a hot (*ca.* 100°) aqueous solution of the corresponding methiodide upon addition of an aqueous sodium fluoborate solution. Most of these fluoborates, **4**, melt sharply *in vacuo* without spontaneous decomposition (unlike the corresponding methiodides) but they do decompose slowly on prolonged heating at temperatures just above their melting points.

The main difficulty associated with the conversion of the methiodides into the corresponding fluoborates was concurrent hydrolysis. Acetophenone *N,N,N*-trimethylhydrazonium iodide (**3a**) rapidly underwent base-catalyzed hydrolysis[6a,13] to regenerate the original ketone and the water soluble *N,N,N*-trimethylhydrazinium iodide. The hydrolysis during conversion of **3** to **4** in the present study could in some instances be minimized by rigorously controlling the pH of the aqueous sodium fluoborate solution. Aqueous solutions of technical sodium fluoborate had a pH of *ca.* 4, which explains the accelerated rate of hydrolysis of certain quaternary hydrazonium iodides. The addition of dilute sodium hydroxide to this sodium fluoborate solution (to a pH of 7.0) resulted in excellent yields for most conversions.

The ketone *N,N,N*-trimethylhydrazonium iodides, with a benzyl group attached to the >C=N group (*e.g.*, **3p**), were rapidly hydrolyzed to the ketones even when treated with the neutral fluoborate solution. The increased rate of hydrolysis for these compounds is probably due to the facile tautomerization to the enamine, which is known to hydrolyze easily.[14]

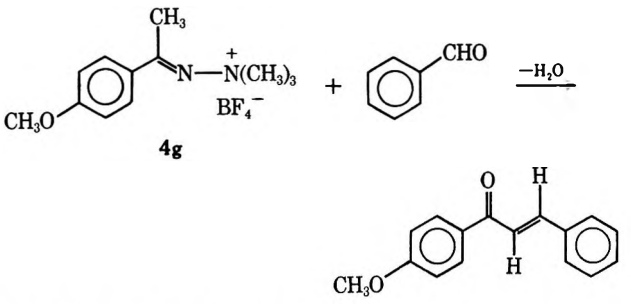
Pyrolysis of Quaternary Hydrazonium Derivatives.—In this study all ketone *N,N,N*-trimethylhydrazonium fluoborates (**4**) contained an α-methylene to >C=N, and were pyrolytically decomposed at temperatures above their melting points either *in vacuo*, suspended in inert solvents, or in a dry nitrogen stream. The tarry residues gave 30–60% of the symmetrically disubstituted pyridine.

The pyrolysis conditions for most fluoborates **4** can be varied considerably with little effect on the overall yield of the pyridine products. When acetophenone *N,N,N*-trimethylhydrazonium fluoborate (**4a**) was pyrolyzed in a high vacuum system, 2,6-diphenylpyridine can be isolated, but, in light of the violently exothermic character of this reaction and rapid evolution of gases, this method was quite limited to sample size. Pyrolytic decomposition of **4a** by suspension in an "inert" refluxing solvent (*i.e.*, cumene, bp 150–155°) offered

(13) M. Avaro, J. Levisalles, and H. Rudler [*Chem. Commun.*, 445 (1969)] have taken advantage of this facile hydrolysis after use of *N,N*-dimethylhydrazones as protection for aldehydes and ketones.

(14) C. R. Hauser, H. M. Taylor, and T. G. Ladford [*J. Amer. Chem. Soc.*, **82**, 1786 (1960)] reported the facile hydrolysis of α-dimethylaminostilbene to generate deoxybenzoin.

no apparent advantage, since the hydrazonium fluoborates were not appreciably soluble in nonpolar solvents even at elevated temperatures. The prolonged refluxing of these fluoborates (**4**) in lower boiling solvents (*e.g.*, ethanol) has been shown to give negligible yields of the pyridine derivatives.[15] Other solvents were not investigated due to the possible occurrence of undesirable side reactions as was observed with benzaldehyde. The pyrolysis of 4′-methoxyacetophenone *N,N,N*-trimethylhydrazonium fluoborate (**4g**) in refluxing



benzaldehyde (bp 180°) afforded 2-benzal-4′-methoxyacetophenone, which was formed by simple condensation.

The general method for these exothermic pyrolysis reactions, adopted in order to isolate the gases liberated, was decomposition of a "train"[16] of the fluoborate, **4**. The fluoborate closest to the nitrogen inlet was carefully heated, until decomposition commenced; the nitrogen swept the amine gases and inorganic sublimates into the series of cold traps. After the initial reaction, the residual tar in the pyrolysis tube was heated to 200–250° for several additional minutes.

Pyrolysis of **4a** in this manner[16] gave a white sublimate which was identical with an authentic sample of ammonium fluoborate. The trapped gases were bubbled through an ethereal methyl iodide solution from which tetramethylammonium iodide precipitated. To distinguish between alkylation of ammonia and/or any of the methyl amines, the carrier gas was passed through a saturated hydrogen chloride ether solution; a mixture of hygroscopic amine hydrochlorides precipitated. The nmr spectrum of this amine hydrochloride mixture showed the presence of three major singlets corresponding to the proton resonances for ammonium chloride, dimethylamine hydrochloride (δ 2.84, NCH_3) and trimethylamine hydrochloride (δ 2.96, NCH_3); there was no (<0.5%) evidence for methylamine hydrochloride (δ 2.70, NCH_3).

The residual tar from the pyrolysis of **4a** was analyzed by glc and tlc, both of which indicate one major product, 2,6-diphenylpyridine, along with traces of acetophenone and 2,6-diphenyl-3-methylpyridine; these are the only identifiable organic products.

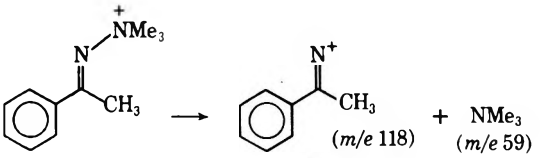
The major product from pyrolysis of **4l** was 2,6-diphenyl-3,5-dimethylpyridine, thus indicating that no rearrangement of the 3-carbon side chain had occurred during pyrolysis. This result suggested that the γ carbon (C_4) of the newly formed pyridine ring is derived from the trimethylamine moiety. The mass spectrometric studies suggest that there is a substantial amount of N–N cleavage as a primary process for the cation during pyrolysis of the fluoborates. This is indicated by a strong 59 *m/e* ion peak, presumed due to trimethylamine, in the low voltage spectrum of **4a** (Table II). This route could represent a

TABLE II
PARTIAL LOW VOLTAGE[a] MASS SPECTRUM OF **4a**

m/e	Rel intensity		*m/e*	Rel intensity	
45	112	C_2H_7N	142	5	
58	6		143	3	
59	68	C_3H_9N	147	1	
60	3		148	1	
104	2		149	2	
106	2		162	10	$C_{10}H_{14}N_2$
119	19	C_6H_9N	231	120	M^+, $C_{17}H_{13}N$
120	2		232	19	
128	3		233	3	
130	1		244	3	
131	7	C_9H_9N	245	7	$C_{18}H_{15}N$
132	1		246	2	

[a] 12 eV operating voltage.

reaction competitive with those leading to pyridine ring formation or might be a necessary preliminary step before transfer of carbon (destined to be the pyridine γ carbon) from the trimethylamine moiety to the acetophenoniminium residue, i. Intermolecular



i

alkyl exchange between a quaternary salt and a tertiary amine[17] is a reasonably facile reaction at these temperatures.

Radiolabeling experiments were then conducted to test the hypothesis that the pyridine γ carbon is constructed from the trimethylamine moiety. Pyrolysis of **4a**-*N*-^{14}C afforded the labeled 2,6-diphenylpyridine, in which the theoretical one-third incorporation was experienced. Other ^{14}C sources (*N,N,N*-trimethylhydrazinium-^{14}C fluoborate and tetramethylammonium fluoborate) were used; negligible incorporation of the radiolabel was experienced. The overall conclusion is that intermolecular radiolabeling did not occur to any appreciable extent in these experiments, suggesting either that the incipient γ carbon is transferred intramolecularly within the ketone *N,N,N*-trimethylhydrazonium fluoborate or that separation of the trimethylamine moiety before transfer of carbon is insufficiently complete to allow significant exchange with other quaternary nitrogen derivatives. The latter result would also be observed if one carbon on the leaving trimethylamine moiety was chemically different, incapable of simple exchange and was in fact the incipient γ carbon of the pyridine ring.

Several experiments were conducted in which mixtures of two different ketone *N,N,N*-trimethylhydrazonium fluoborates were pyrolyzed to determine the extent of formation of unsymmetric 2,6-diarylpyridines. For equimolar mixtures of **4a** and **4g**, the molar product distribution was 1:2:1 of 2,6-diphenylpyridine, 2-

(15) R. Widmer, K. S. U., private communication.

(16) The "train" was composed of a horizontal Pyrex tube fitted with an inlet for an inert gas, followed by a series of traps cooled in liquid nitrogen.

(17) S. Hunig and W. Baron, *Chem. Ber.*, **90**, 395 (1957).

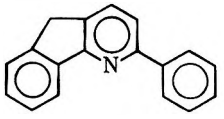
TABLE III

MASS SPECTRAL DATA FOR THE ACETOPHENONE DERIVED SEQUENCE[a]

m/e	5a	4a	3a[b]	2a	m/e	5a	4a	3a	2a	m/e	5a	4a	3a	2a
247			4		153	2	1			101	5	3		
246			5		152	2	1			100	1			
245		1.6[c]	6		148				2.3	91	1.3			4.3
244		4.0	5		147				21.7	90			5	
233	2.4	3.0	8		146			8	1.2	89	2.3		8	
232	27.5	16	10		142			100		88	2	2		
231	100[d]	100[d]	61		140			5		81				1.7
230	70	50	30		133			5	2	80				2.5
229	5	4			132		2	11	18.7	79		5		5.5
228	7	4			131		3[f]	10	3.0	78	1.5	4	10	10
227	1	1			130		2	10	2.0	77	6.4	14	41	40
219		2			129			5		76	3.2	7	10	5
218			3		128	3.2		61		75	2	3	5	2
217			5		127	6.2		45		74	1.2			
215		1			126	2.7				71				
208		2			121	1.5				63	1.5		6	2
207		7	10		120		1	5	2.5	59		10		
206		1			119		8[g]	19	6.0	58		20	52	
204	2.7	2			118		2	14	18	57		2	5	
203	3.0	3.0			117			7	2	54		1.5		
202	7.1	6	6		116	2.9	2	7		52	1.2	1	5	2
201		1			115.5	13	11	6		51	4.0	7	17	14.7
178		1			115	5	6	11		50	1.8	2	8	5
177		1			114.5	5	3			49		21		
176		1[e]			114	7.6	6	5		48		2		
163			9	10.3	107			7		45		18		20
162			23	100	106	2.3	1	6	8	44	1.5	30	15	35
161			6	7.6	105		2	13	1.5	43		6	33	7
160			33		104		20[h]	52	13	42		10	8	16
159			35		103	2.3	3[i]	26	11	41	1.1	2	31	3
158			10		102.5	2				40		4		2
154	4	5	6		102	12	6	23	1.3	39	1.6	3		

[a] Direct insertion method at 200° inlet temperature, 70 eV, 100 μA. [b] Other fragments: m/e (rel intensity) 399 (2), 397 (2), 396 (4), 385 (5), 384 (2), 383 (2), 382 (2), 373 (4), 372 (5), 371 (4), 370 (3), 359 (3), 358 (4), 357 (5), 356 (6), 346 (8), 322 (5), 321 (8), 308 (5), 307 (5), 306 (2), 263 (5), 261 (5), 260 (5), 259 (4); ions of relative intensity ≥2%. [c] High resolution data: $C_{18}H_{15}N$ (calcd 245.12044, found 245.12057). [d] High resolution data: $C_{17}H_{13}N$ (calcd 231.10479, found 231.10472). [e] High resolution data: $C_{11}H_{16}N_2$ (calcd 176.13134, found 176.13153). [f] High resolution data: C_9H_9N (calcd 131.07350, found 131.07374). [g] High resolution data: C_8H_9N (calcd 119.07349, found 119.07339). [h] High resolution data: C_7H_6N (calcd 104.05002, found 104.04945). [i] High resolution data: C_8H_7 (calcd 103.05477, found 103.05311) and C_7H_5N (calcd 103.04220, found 103.04242).

2-phenyl-6-(4-methoxyphenyl)pyridine, and 2,6-di(4-methoxyphenyl)pyridine, respectively. This statistically expected product distribution was not observed from pyrolysis of intimate mixtures of **4a** with 1-indanone *N,N,N*-trimethylhydrazonium fluoborate;[3] rather, a ratio of 0.16:0.8:1 was obtained for **5a**, 2-phenyl-5*H*-indeno[1,2-*b*]pyridine (**6**), and 1,12-dihydrodiindeno[1,2-*b*:2′,1′-*e*]pyridine (**7**), respectively. These



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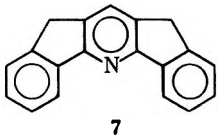

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results demonstrate that the reaction medium is essentially homogeneous (*i.e.*, there is no restriction of free movement of what must be two separate intermediates contributing to the final 2,6-diarylpyridine product) and, furthermore, that these intermediates have a significant lifetime even in condensed phases.

Pyrolysis of either acetophenone *N,N,N*-trimethylhydrazonium iodide (**3a**) or the corresponding tosylate gave 2,6-diphenylpyridine (**5a**) in less than 2% yield as well as resinous oils which were not further investigated. Analysis of sublimates from the iodide pyrolysis indicated significant amounts of quaternary ammonium iodide salts; the quantitative composition was not determined.

Pyrolytic Mass Spectrometric Study. Formation of and Evidence for the Reactive Intermediates.—Small samples of the quaternary salts were pyrolyzed in the high vacuum of a mass spectrometer ion source by direct introduction to the heated source block. The pyrolysis mass spectra were in general reproducible for comparable source pressures, temperatures, and sample size and if scan times following sample introduction were the same. A rigorous investigation of the lifetimes of intermediates by time-resolved techniques has been made, from which several qualitative observations for specific intermediates are outlined. At source pressures ($p < 10^{-5}$ Torr) intermediates with lifetimes comparable to analysis scan times (1–15 sec) should be preserved in sufficient amounts for their mass spectra to be displayed along with those of stable products. Ion intensities of spectra thus produced may be corrected by selective subtraction of the contributions to the same ions from stable products.

The spectra of analytical samples of known pyrolysis products were obtained under closely similar conditions in the same spectrometer used in the pyrolysis studies. The spectra of the *N,N*-dimethylhydrazones (**4a**, Table III) exhibit features at low mass numbers

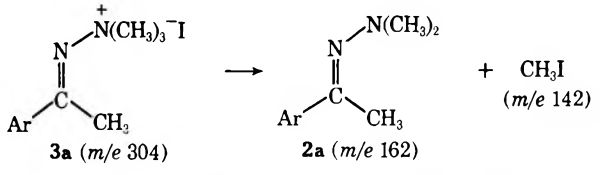
analogous to those reported by Goldsmith and Djerassi[18] in their study of hydrogen rearrangement and fragmentations of aliphatic ketone *N,N*-dimethylhydrazones. The principal fragmentation processes appear to be either loss of one or more methyl groups from the molecular ion or N–N cleavage. The latter process may also involve 1,3-hydrogen transfer between the two fragments.

The 2,6-diarylpyridines are extremely stable compounds. This is demonstrated by high intensities for molecular ions, doubly and triply charged ions, and by relatively low intensities for all fragment ions (**5a**, see Table III).

Acetophenone *N,N,N*-Trimethylhydrazonium Iodide (3a).—Strong ion intensities are observed in the pyrolysis mass spectrum of acetophenone *N,N,N*-trimethylhydrazonium iodide (**3a**, Table III) at *m/e* values of 231, 160–162, 142, 128, 127, 104, 77, and 58. Ions at *m/e* values of 231, 162, 142, and 128 represent **5a, 2a,** methyl iodide, and hydrogen iodide, respectively; this may be inferred by their persistence in low-voltage spectra, by exact mass measurement, and by isolation from pyrolysis residues.

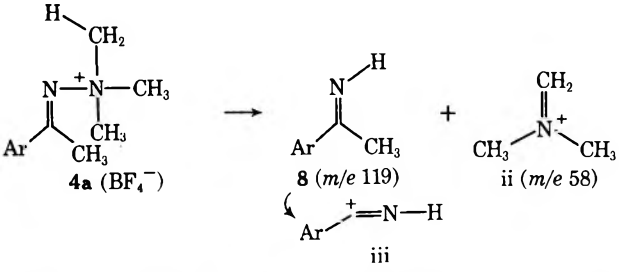
2,6-Diphenylpyridine (**5a**) is readily identified as a minor component by the molecular ion pattern; it is confirmed by a strong metastable at 229 (231 → 230) and characteristic doubly charged ion peaks at 114.5 115.5. Acetophenone *N,N*-dimethylhydrazone (**2a**) is also supported by well characterized metastable ion peaks at 160 (162 → 161), 133.4 (162 → 147, loss of CH_3), and 118.6 (147 → 132, loss of second CH_3) and the occurrence of all expected fragment ions for this compound.

The presumption that acetophenone *N,N*-dimethylhydrazone and methyl iodide must arise by simple nucleophilic displacement is supported by a metastable ion peak at ~ 86.4 (304 → 162). This process for the quaternary iodides (*e.g.*, **4a**) accounts for the major fragmentation pathway.



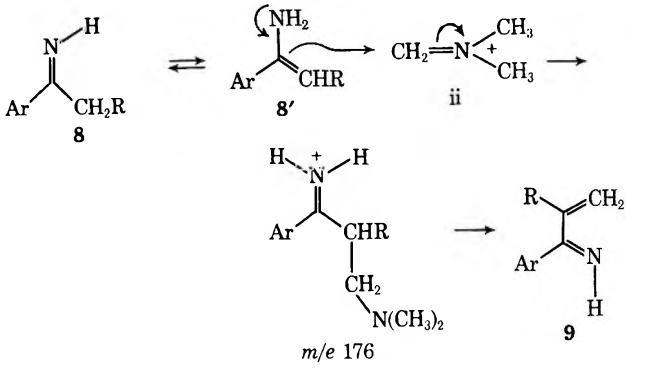
3a (*m/e* 304) **2a** (*m/e* 162)

Acetophenone *N,N,N*-Trimethylhydrazonium Fluoborate (4a).—Although the construction of the pyridine ring is a minor route in the pyrolytic mass spectrum of **3a**, the formation of substituted pyridines from the corresponding fluoborates (**4a**) constitutes the major pathway. Construction of the pyridine γ carbon by internal transfer of an *N*-methyl group may be envisioned in several ways on the basis of ions which are present in the pyrolysis mass spectra of all the quaternary salts, but especially the fluoborates. The acetophenone *N,N,N*-trimethylhydrazonium cation is expected to undergo simple N–N cleavage as the most likely thermal process independent of interactions with the anion. This would give a stable product trimethylamine, *m/e* 59, as well as the hypothetical reactive intermediate, acetophenoniminium cation, i, *m/e* 118. Alternately, 1,3-hydrogen migration may occur with N–N cleavage to give dimethylmethyleneammonium cation, ii, *m/e* 58, and the imine, **8**, *m/e* 119. Low-voltage mass spectra of acetophenone *N,N,N*-trimethylhydrazonium fluoborate (as well as iodide and tosylate) all have prominent ion peaks at *m/e* values of 119 and 58. Subsequent methyl loss by electron-impact fragmentation of imine **8** would give an *m/e* 104 species, iii, which is supported by a meta-



stable ion at 90.0 (119 → 104). Exact mass measurement of both the 119 and 104 ions is consistent with the proposed composition for these ions (footnotes, Table III). There is inherent in this datum the implication that the imine **8** has a lifetime sufficient to undergo subsequent rearrangement and reaction. Tautomerization of **8** to α-aminostyrene (**8'**) followed by electrophilic alkylation of the resulting enamine with Mannich reagent, dimethylmethyleneammonium cation,[19] ii, is proposed as a convenient mechanistic route to the incipient pyridine γ carbon. This condensation product readily eliminates dimethylamine and a proton to give the diene **9** as a potential reactive intermediate (Scheme I). Evidence for **9** exists as

SCHEME I



the ion at *m/e* 131 in the spectra of all the quaternary salts. This ion is absent in the spectrum of 2,6-diphenylpyridine; therefore, it does not arise by electron-impact fragmentation of this product.

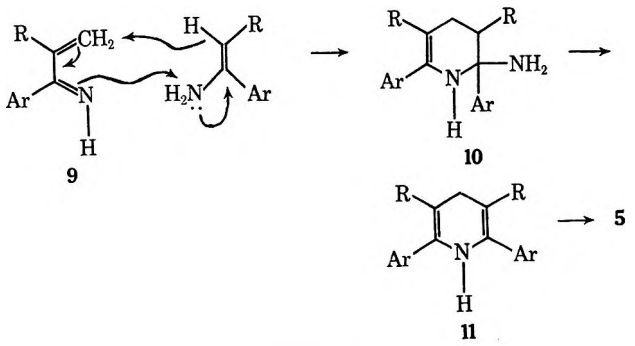
Although acetophenone *N,N*-dimethylhydrazone has an ion peak at *m/e* 131 in its spectrum, this is an insufficient source of this ion in spectra of quaternary salts. Even though the iodide and tosylate spectra have as a significant feature the molecular ion (*m/e* 162) for acetophenone *N,N*-dimethylhydrazone, the *m/e* 131 peak exceeds the expected intensity if it were to be derived as a fragment ion from this hydrazone.

In a series of mass spectra obtained by rapid scanning immediately following pyrolysis of quaternary salts in the ion source, the intensity of the *m/e* 131

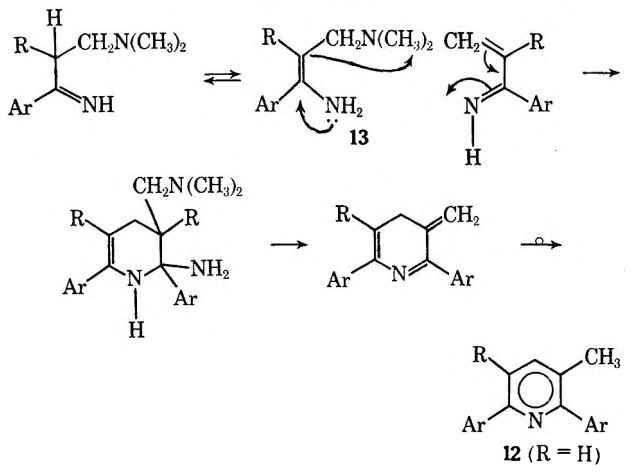
(18) D. Goldsmith and C. Djerassi, *J. Org. Chem.*, **31**, 3661 (1966).

(19) Recently, Eschenmoser, *et al.* [*Angew. Chem., Int. Ed. Engl.*, **10**, 330 (1971)], have isolated (80%) this methyleneammonium salt, ii (I^-). This Mannich reagent can be recrystallized and sublimed at reduced pressure without decomposition.

SCHEME II



SCHEME III



peak may be seen to rise and then fall off to a much greater extent than other ions identifiable as stable molecular species (*m/e* 231, 162, 142, 128, and 59). Furthermore, there is a rough inverse correlation between the intensity of 131 and 231 ion peaks, the latter rising and persisting after the 131 ion peak has nearly vanished during repetitive scanning.

It is our belief, therefore, that **9** (*m/e* 131) represents one of the reactive intermediates, which will supply the γ carbon of the pyridine nucleus during the pyrolysis of the ketone *N,N,N*-trimethylhydrazonium salts.

Mechanistic Construction of the Pyridine Nucleus.—The mechanism envisaged to account for the final construction of the pyridine nucleus can be considered a ramification of the Hantzch synthesis[4a] by the recombination of the evidenced fragments (Scheme II). The reunion of the electron-rich β carbon of the enamine **8′** and **9** by a Michael-type addition gives a dihydropyridine (**11**) after the elimination of ammonia. There is no mass spectral evidence for this cycloaddition intermediate (**10**) due to the facile loss of ammonia under the reaction temperatures. Aromatization of the pyridine nucleus can occur by "transfer" of hydrogen to molecules with isolated double bonds,[20] *e.g.*, with the Mannich reagent ii, or by loss of molecular hydrogen.[21] Isolation of trimethylamine has been accomplished, although there is no direct evidence to support this proposed reductive sequence.

The 2,6-diphenyl-3-methylpyridine (**12**) can arise from a similar Michael-type addition of the enamine (**9**) and the tautomer of its precursor (**13**), followed by loss of ammonia and dimethylamine, then aromatization (Scheme III).

The mass spectrum data and the detailed analyses of the products from this pyrolysis reaction have substantiated the Hantzch-type mechanistic scheme for the production of the pyridine nucleus. In our studies, as well as in many historical examples, the actual isolation of these proposed intermediates has been difficult to realize. Additional studies on the trapping of these elusive intermediates are currently underway on other closely related systems.

(20) R. L. Frank and R. P. Seven, *J. Amer. Chem. Soc.*, **71**, 2629 (1949).

(21) G. J. Janz, R. G. Ascah, and A. G. Keenan, *Can. J. Res.*, **25B**, 272 (1947); G. J. Janz and A. G. Keenan, *ibid.*, **25B**, 283 (1947).

Experimental Section[22]

Reagents.—Anhydrous *N,N*-dimethylhydrazine (99%), iodomethane (reagent, 99+%), and sodium fluoborate (technical grade) were obtained from Matheson Coleman and Bell. Radioactive methyl-^{14}C iodide was purchased from New England Nuclear Corp., Boston, Mass. Samples of the starting carbonyl compounds were available from ordinary commercial sources and were purified by redistillation or recrystallization prior to use.

Methyl iodide had mass spectrum (70 eV) *m/e* (rel intensity) 143 (0.69), 142 (100), 141 (7.2), 140 (2.1), 139 (2.3), 128 (1.7), 127 (13.5), and 15 (17.9).

General procedure for the preparation of dimethylhydrazones has been previously described in detail.[9] Properties of various *N,N*-dimethylhydrazones which have not been previously reported[9] are cited in Table I.

General Preparation of Ketone *N,N,N*-Trimethylhydrazonium Iodides.[24] **Method A.**—A mixture of acetophenone *N,N*-dimethylhydrazone (5.0 g, 0.033 mol) and excess methyl iodide in anhydrous ether (20 ml) was allowed to stand for several days at room temperature. The crude product was filtered, washed with ether, dried *in vacuo*, and recrystallized from absolute ethanol–ethyl acetate to afford 6.3 g (67%) of acetophenone *N,N,N*-trimethylhydrazonium iodide: mp 146° dec; nmr (D_2O) δ 2.6 (CCH_3, s, 3 H), 3.5 [$N^+(CH_3)_3$, s, 9 H], and *ca.* 7–8 (m, Ar H, 5 H); uv (EtOH) λ_{max} 215 mμ (shoulder) and 249 (ϵ 13,300); mass spectrum, see Table III.

Method B.—The following preparation of **3a** will exemplify the general procedure. Acetophenone *N,N*-dimethylhydrazone (10 g, 0.066 mol) and excess methyl iodide in anhydrous methanol (50 ml) were refluxed under nitrogen for 6 hr. After cooling, cold anhydrous ether was added; the crude precipitated methiodide was collected and recrystallized. The yield was increased (87%); samples prepared by method B were identical in all respects with those from prepared by method A.

Acetophenone *N,N,N*-Trimethylhydrazonium Tosylate.—An ethanolic solution of acetophenone *N,N*-dimethylhydrazone (10 g, 0.066 mol) and methyl *p*-toluenesulfonate (15 g, 0.081 mol) was allowed to stand at room temperature for 2 days; the mixture was then poured into anhydrous ether. The crude tosylate was filtered and recrystallized from absolute ethanol, affording 18.2 g (79%) of acetophenone *N,N,N*-trimethylhy-

(22) All melting points were taken in sealed capillaries with a Thomas-Hoover Unimelt and are uncorrected. The infrared spectra were determined with either a Perkin-Elmer 237-B or 337-B spectrophotometer and the ultraviolet data were recorded on a Cary 14 spectrometer. Refractive indices were obtained with a Bausch and Lomb Abbé-type refractometer. Nmr spectra were obtained on a Varian Associates Model A-60 spectrometer. The chemical shift values are expressed in δ (parts per million) relative to a tetramethylsilane internal standard. Radioactive samples were assayed on either a Packard Tri-Carb liquid scintillation spectrometer system Series 3000, or Model 3003 (for those compounds which were soluble, without decomposition or coloration, in Bray's Cocktail[23]) or a Nuclear-Chicago thin window gas flow detector Model D47, equipped with a Nuclear-Chicago automatic sample changer Model C110B. Mass spectra were measured by Mr. Nathan Ingber or Mr. Robert Wadsworth of the Standard Oil Co., Cleveland, Ohio, on their CEC 21-103C spectrometer equipped with an MS 7500 Universal heated inlet system and in these laboratories on an A. E. I. MS-12 medium resolution mass spectrometer; spectra were 70 eV, electron-impact fragmentation unless otherwise indicated. The microanalyses were performed by Spang Microanalytic Laboratories, Ann Arbor, Mich., and Galbraith Laboratories, Inc., Knoxville, Tenn.

(23) G. A. Bray, *Anal. Biochem.*, **1**, 279 (1961).

(24) The yields and physical constants are quoted in Table I.

drazonium tosylate: mp 175–176° dec; nmr (D_2O) δ 3.44 [$N^+(CH_3)_3$, s, 9 H], 2.54 (CCH_3, s, 3 H), 2.13 ($ArCH_3$, s, 3 H), and *ca.* 7–8 (m, ArH, 9 H).

Anal. Calcd for $C_{18}H_{24}N_2SO_3$: C, 62.04; H, 6.94; N, 8.04. Found: C, 61.97; H, 6.87; N, 8.00.

General Preparation of Ketone *N,N,N*-Trimethylhydrazonium Fluoborates.—The following preparation of acetophenone *N,N,N*-trimethylhydrazonium fluoborate will exemplify the procedure.[24]

A hot aqueous solution[25] of sodium fluoborate (30 g) was slowly added to a refluxing solution of acetophenone *N,N,N*-trimethylhydrazonium iodide (30 g, 0.098 mol) dissolved in minimum water to ensure complete dissolution. The mixture was then cooled to room temperature; the crude crystalline product was filtered, dried *in vacuo*, and recrystallized from acetone–absolute ethanol, giving 25.5 g (96%) of acetophenone *N,N,N*-trimethylhydrazonium fluoborate: mp 153–154° dec; nmr (D_2O) δ 2.75 (CCH_3, s, 3 H), 3.60 [$N^+(CH_3)_3$, s, 9 H], and a complex aromatic proton region; uv (EtOH) λ_{max} 214 mμ (ε 16,900) and 248 (9850); mass spectrum (see Table III).

Attempted Synthesis of Deoxybenzoin *N,N,N*-Trimethylhydrazonium Fluoborate.—A hot aqueous solution of deoxybenzoin *N,N,N*-trimethylhydrazonium iodide (15.4 g, 0.0405 mol) was added to the aqueous sodium fluoborate solution;[25] after cooling to ice bath temperature, the pale yellow oil which separated was worked up and distilled, giving 4.1 g (52%) of deoxybenzoin, bp 136–138° (0.25 mm). The physical and spectral data were identical with those of the starting ketone.

Pyrolysis of Acetophenone *N,N,N*-Trimethylhydrazonium Fluoborate. Method A.—Acetophenone *N,N,N*-trimethylhydrazonium fluoborate (20 g, 0.0758 mol), which was dried *in vacuo* at 40° for several days, was heated to decomposition (*ca.* 200°) in 5-g quantities in a pyrolysis tube (1 × 12 in.) flushing continuously with a slow stream of dry nitrogen. During the pyrolysis, the liberated gases and a white sublimate were trapped in two liquid nitrogen gas traps. After cooling, extraction of the pyrolysis vessel with benzene afforded a viscous red oil (9.371 g), along with an inorganic residue which was insoluble in benzene.

Column chromatography of this crude oil (2.00 g) was performed on Brinkmann silica gel G (¾ in. × 3 ft) eluting with a mixture of *n*-hexane, benzene, and ethyl acetate (85:5:10, respectively) under nitrogen collecting 15-ml fractions. Fractions 1 to 10 upon concentration yielded 100 mg of acetophenone: bp 201°; ir (neat) 1680 (C=O) and 1265 cm^{-1}; nmr (CCl_4) δ 2.0 (CCH_3, s); 2,4-dinitrophenylhydrazone mp 249° (lit.[26] mp 250°). Fractions 12–18 (R_f 74)[27] upon concentration afforded a white solid which was recrystallized from low-boiling petroleum ether, giving 867 mg (49.5%) of the crystalline 2,6-diphenylpyridine: mp 82–83° (lit.[28] mp 82°); picrate mp 171° (ethanol) (lit.[29] mp 169°); uv (EtOH) λ_{max} 243 mμ (ε 27,600), 286 (10,500), 302 (12,200); mass spectrum (see Table III). Fractions 18–22 (R_f 72)[27] upon concentration afford a viscous yellow oil, which was distilled in a molecular still affording 108 mg (5.5%) of 3-methyl-2,6-diphenylpyridine: bp 150–160° (0.5 mm) [lit.[30] bp 253–255° (25 mm)]; nmr ($CDCl_3$) δ 2.22 ($ArCH_3$, s, 3 H); mass spectrum *m/e* (rel intensity) 245.12057 (M^+, 53), 244 ($M - 1^+$, 100), 230 ($M^+ - CH_3$, 30), 77 (C_6H_5, 7).

Anal. Calcd for $C_{18}H_{15}N$: C, 88.12; H, 6.17; N, 5.71. Found: C, 88.05; H, 6.12; N, 5.71.

Fractions 24–44 (R_f 52)[27] upon concentration gave an unidentified red oil (52 mg). Fractions 45–180 yielded no identifiable compounds comprising of polymeric residues remaining on the column. Attempted elution of this material afforded no discernible organic compounds.

The white sublimate, produced during the pyrolysis, was identical with an authentic sample of ammonium fluoborate; on comparison ir and nmr spectrum properties were superimposible.

The gas, after removal of the sublimed ammonium fluoborate, was warmed slowly and bubbled through a solution of anhydrous methyl iodide in ether. The white quaternary salt was collected, dried *in vacuo*, and recrystallized from deuterium oxide, giving tetramethylammonium iodide: mp <300° dec; nmr (D_2O) δ 3.26 [$N(CH_3)_4$, t, J = 0.5 Hz], which is identical with the nmr spectrum of an authentic sample.

Anal. Calcd for $C_4H_{12}NI$: C, 24.04; H, 6.18; N, 6.94. Found: C, 23.91; H, 6.25; N, 6.84.

A second sample of gas was bubbled into anhydrous hydrogen chloride (*ca.* 5%) dissolved in anhydrous ether. The white precipitate which formed was carefully filtered (with complete exclusion of moisture) and dried *in vacuo*, giving a hydroscopic mixture of amine hydrochlorides, nmr (D_2O) δ 4.70 (s, NH), 2.95 [s, $^+N(CH_3)_3$], and 2.80 [s, $^+N(CH_3)_2$]. These peaks corresponded to nmr spectra (D_2O) of authentic samples of ammonium chloride, trimethylamine hydrochloride, and dimethylamine hydrochloride.

The other substituted diarylpyridines are listed in Table I and were prepared in the same manner, except where noted.

Method B. Pyrolysis in Cumene as Solvent.—Acetophenone *N,N,N*-trimethylhydrazonium fluoborate (10 g, 0.038 mol) in cumene (20 g, bp 150–155°) as solvent was slowly heated to about 154–150°; the exothermicity of the reaction then causes the solution to reflux for *ca.* 1 min. The mixture was refluxed for an additional 1 hr. After cooling, the solution was decanted from an inorganic residue and concentrated *in vacuo*, leaving a crude residue which was chromatographed on Merck alumina (¾ in. × 2 ft) eluting with 1% benzene in low-boiling petroleum ether. Upon concentration and recrystallization of the eluent, 2,6-diphenylpyridine (mp 81–82°) was obtained (55%); mixture melting point with authentic sample was undepressed.

Pyrolysis of Acetophenone *N,N,N*-Trimethylhydrazonium Iodide.—Acetophenone *N,N,N*-trimethylhydrazonium iodide (20 g, 0.067 mol) was pyrolyzed as described under method A. 2,6-Diphenylpyridine (mp 80°) was isolated (1.3%) from the dark polymeric tar. No other organic compounds were isolated from the polymeric residue.

Pyrolysis of acetophenone *N,N,N*-trimethylhydrazonium tosylate was conducted as previously described under method A. 2,6-Diphenylpyridine (mp 81°) was isolated in less than 2% yield from the black viscous residue; no other discernible organic products were detected.

2-Phenyl-6-(4-methoxyphenyl)pyridine.—Acetophenone *N,N,N*-trimethylhydrazonium fluoborate (5.71 g, 18.6 mmol) and 4′-methoxyacetophenone *N,N,N*-trimethylhydrazonium fluoborate (6.4 g, 18.6 mmol) were mechanically mixed and pyrolyzed as described in method A. The concentrated benzene extract was chromatographed on Merck alumina (¾ in. × 2.2 ft); the first fraction was eluted with 2% benzene in petroleum ether. After concentration and recrystallization, only 2,6-diphenylpyridine (mp 78–80°) identical with previously obtained sample was isolated. A second component was eluted with 20% benzene in petroleum ether, giving, upon concentration, 2-phenyl-6-(4-methoxyphenyl)pyridine, which upon recrystallization from petroleum ether (bp 60–70°) gave an analytical sample: 0.335 g; mp 125° (lit.[31] mp 119°); nmr ($DCCl_3$) δ 3.78 ($ArOCH_3$, s, 3 H); uv (EtOH) λ_{max} 525 mμ (ε 22,400), 274 (18,000), 289 (15,000), and 308 (11,500).

Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.37. Found: C, 82.77; H, 5.79; N, 5.29.

A third component was eluted with 50% benzene in petroleum ether, yielding 2,6-di(4-methoxyphenyl)pyridine (mp 189–190°; recrystallization from petroleum ether (bp 60–80°) raised the melting point to 197–198°): nmr ($DCCl_3$) δ 3.89 ($C_{aromatic}OCH_3$, 6 H, s); uv (EtOH) λ_{max} 273 mμ (ε 31,200) and 316 (14,350).

3,5-Dimethyl-2,6-diphenylpyridine.—Propiophenone *N,N,N*-trimethylhydrazonium fluoborate (17 g, 0.062 mol) was pyrolyzed and worked up as described above in method A. Recrystallization from petroleum ether of the crude eluent gave 4.5 g (50%) of the white crystalline 3,5-dimethyl-2,6-diphenylpyridine: mp 136–137° (lit.[32] mp 134–135°); nmr (CCl_4) δ 2.36 ($ArCH_3$, d, J = 0.5 Hz, 6 H); uv (EtOH) λ_{max} 233 mμ (ε 20,000), 250

(25) The aqueous sodium fluoborate solution was prepared by assuring neutral pH (*i.e.*, addition of either dilute sodium hydroxide or fluoboric acid), then filtration to remove all insoluble salts. Rapid hydrolysis of the quaternary salt occurs, if neutrality is not rigorously maintained.

(26) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," Wiley, New York, N. Y., 1964, p 363.

(27) R_f values were determined by thin layer chromatograph using Brinkmann Silica Gel G eluting with column solvent system.

(28) D. Bryce-Smith and A. C. Skinner, *J. Chem. Soc.*, 577 (1963). We thank Professors Bryce-Smith and Skinner for a sample of authentic 2,6-diphenylpyridine.

(29) M. Scholtz, *Ber.*, **28**, 1726 (1895).

(30) M. Scholtz, *ibid.*, **32**, 1935 (1899).

(31) M. Scholtz and W. Meyer, *ibid.*, **43**, 1861 (1910).

(32) V. Galiah and A. Ekambaram, *J. Indian Chem. Soc.*, **32**, 274 (1955).

(shoulder), 288 (9880); mass spectrum (mol wt) calcd 259, found 259.

2,6-Di[2-(6-methylpyridyl)]pyridine.—2-Acetyl-6-methylpyridine *N,N,N*-trimethylhydrazonium fluoborate (10 g, 0.036 mol) was pyrolyzed as described above in method A. The black viscous oil from the pyrolysis reactor was treated with aqueous sodium hydroxide (5 *N*, 2 ml), extracted with benzene, and concentrated. Purification by elution chromatography on Florosil with benzene afforded a pale yellow solid (mp 162–164°). Recrystallization from benzene–petroleum ether (bp 60–70°) gave 2.2 g (47%) of 2,6-di[2-(6-picolyl)]pyridine: mp 164–165°; nmr ($CDCl_3$) δ 2.62 ($ArCH_3$, s, 6 H), and a complex aromatic proton region including 8.4 (t, J = 4 Hz), 7.17 (t, J = 8 Hz), 7.24 (d, J = 4 Hz), and 7.17 (d, J = 8 Hz); uv (EtOH) λ_{max} 231 mμ (ε 11,700), 242 (11,900), and 289 (22,400).

An ethanolic solution of 2,6-di[2-(6-picolyl)]pyridine was slowly added to a solution of ethanolic ferric chloride, giving an ethanol insoluble, uncharacterized substituted 2,2′,2″-tripyridyl complex, mp 278°.

Attempted Synthesis of 4-Phenyl-2,6-di(4-methoxyphenyl)-pyridine.—A mixture of 4′-methoxyacetophenone *N,N,N*-trimethylhydrazonium fluoborate (5.0 g, 17 mmol) and redistilled benzaldehyde (20 ml) was refluxed for 1 hr. At *ca.* 130–150°, the solution turned dark red with azeotropic distillation of water. The solvent (benzaldehyde) and last traces of water were removed by vacuum distillation, leaving a dark oil. Elution chromatography on Merck alumina with 20% benzene in petroleum ether gave a pale yellow solid, which when recrystallized from petroleum ether afforded 1.0 g (25%) of 2-benzal-4′-methoxyacetophenone: mp 104–105° (lit.[33] mp 106°); nmr ($CDCl_3$) δ 3.88 ($ArOCH_3$, s).

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.67; H, 6.00.

2-Phenyl-5*H*-indeno[1,2-*b*]pyridine.—An intimate mixture of acetophenone *N,N,N*-trimethylhydrazonium fluoborate (6.5 g, 25 mmol) and 1-indanone *N,N,N*-trimethylhydrazonium fluoborate[3] (7.09 g, 25 mmol) was dried *in vacuo* at *ca.* 50° for several hours. The mixture was pyrolyzed as described under method A. The residual pyrolysate was extracted with benzene, concentrated, and chromatographed on alumina. Fraction 1 was eluted with 2% benzene in low-boiling petroleum ether (bp 30–60°, *ca.* 500–1000 ml) and gave 2,6-diphenylpyridine (150 mg, mp 79–80°) which was identical with an authentic sample.

The second fraction was eluted with 20% benzene in petroleum ether (bp 30–60°, 1000 ml) affording 2-phenyl-5*H*-indeno[1,2-*b*]-pyridine (760 mg), mp 120°. Recrystallization gave an analytical sample: mp 126–128°; nmr ($DCCl_3$) δ 3.67 ($ArCH_2$–, s, 2 H) and a complex aromatic region; uv (EtOH) λ_{max} 245 mμ (ε 30,200), 261 (10,800), and 318 (20,500).

Anal. Calcd for $C_{18}H_{13}N$: C, 88.85; H, 5.39; N, 5.76. Found: C, 88.88; H, 5.47; N, 5.72.

The third fraction was eluted with 50% benzene in petroleum ether (1000 ml) giving 10,12-dihydrodiindeno[1,2-*b*:2′,1′-*e*]-pyridine (1.05 g)[3], mp 203° (lit.[34] mp 206–207°).

2,6-Diphenylpyridine-^{14}C.—Acetophenone *N,N,N*-trimethylhydrazonium-^{14}C fluoborate (average activity 1320 cpm/μmol) was prepared in the same manner as unlabeled material, except for substitution of methyl-^{14}C iodide in the initial quaternization. The labeled fluoborate was pyrolyzed; the product was extracted and purified as previously described under method A. Five additional recrystallizations from petroleum ether gave an analytical sample of 2,6-diphenylpyridine-^{14}C: mp 82–83°, average activity 445 cpm/μmol. The ^{14}C ratio in the product, 2,6-diphenylpyridine, relative to the starting fluoborate was 1:2.96.

Pyrolysis of 4′-methoxyacetophenone *N,N,N*-trimethylhydrazonium fluoborate and *N,N,N*-trimethylhydrazonium-^{14}C fluoborate, prepared from the corresponding labeled iodide by precipitation of the less soluble fluoborate, was conducted as previously described under method A; recrystallization of the 2,6-di(4-methoxyphenyl)pyridine from benzene–petroleum ether afforded an analytical sample: mp 189–190°; the ratio of radioactive carbon was 34 cpm/μmol (product) to 635 cpm/μmol (*N,N,N*-trimethylhydrazonium fluoborate) or 5% incorporation of the original radiolabel.

Pyrolysis of 4′-methoxyacetophenone *N,N,N*-trimethylhydrazonium fluoborate and tetramethylammonium-^{14}C fluoborate, prepared from the corresponding labeled quaternary iodide by precipitation of the less soluble fluoborate, was executed as previously described under method A; recrystallization afforded 2,6-di(4-methoxyphenyl)pyridine, mp 190°. The ratio of radioactivity was 0.25 cpm/μmol (product) to 47 cpm/μmol (ammonium salt); the product therefore contains less than 0.5% ^{14}C of the original radiolabel.

Registry No.—**2g**, 13466-32-5; **2k**, 33785-76-1; **2l**, 19679-59-5; **2m**, 33785-78-3; **2n**, 33785-79-4; **2o**, 33785-80-7; **2p**, 33785-81-8; **3a**, 33785-82-9; **3b**, 33785-83-0; **3c**, 33785-84-1; **3d**, 33777-72-9; **3e**, 33777-73-0; **3f**, 33777-74-1; **3g**, 33777-75-2; **3j**, 33777-76-3; **3k**, 33777-77-4; **3l**, 19679-61-9; **3m**, 33777-79-6; **3n**, 33777-80-9; **3o**, 33777-81-0; **3p**, 33777-82-1; **4a**, 10467-41-1; **4b**, 33775-44-9; **4c**, 10467-42-2; **4d**, 33775-46-1; **4e**, 33775-47-2; **4f**, 33775-48-3; **4g**, 33775-49-4; **4j**, 33775-50-7; **4k**, 33775-51-8; **4l**, 10467-43-3; **4m**, 33775-53-0; **4n**, 33775-54-1; **4o**, 33775-55-2; **5a**, 3558-69-8; **5b**, 33777-84-3; **5d**, 33777-85-4; **5e**, 33777-86-5; **5f**, 33777-87-6; **5g**, 21172-80-5; **5j**, 33777-89-8; **5k**, 33777-90-1; **5m**, 33777-91-2; **5o**, 33777-92-3; acetophenone *N,N,N*-trimethylhydrazonium tosylate, 33777-93-4; 3-methyl-2,6-diphenylpyridine, 28489-52-3; tetramethylammonium iodide, 75-58-1; 2-phenyl-6-(4-methoxyphenyl)pyridine, 33777-95-6; 2-benzyl-4′-methoxyacetophenone, 959-23-9; 2-phenyl-5*H*-indeno[1,2-*b*]pyridine, 33777-97-8.

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(33) E. J. Bourne, M. Stacey, J. C. Tatlow, and J. M. Tedder, *J. Chem. Soc.*, 718 (1951).

(34) W. Borsche and H. Hahn, *Justus Liebigs Ann. Chem.*, **537**, 219 (1939).

2-Pyrones from Condensation of β-Keto Esters with 1,3 Diketones in Trifluoroacetic Acid. A Correction of the Literature

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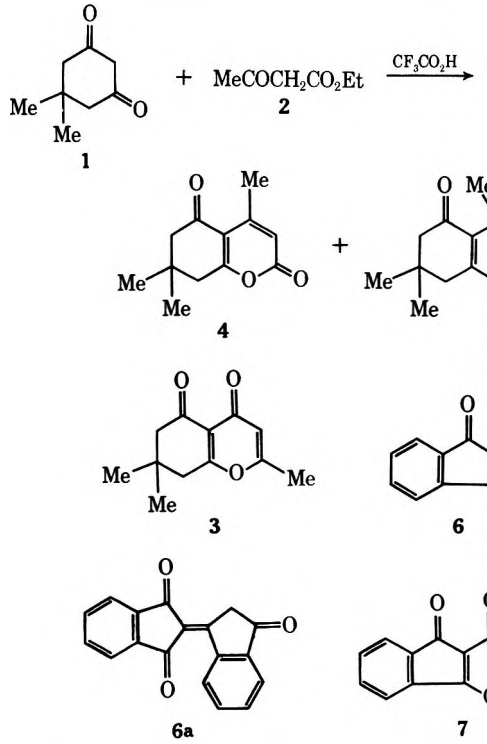
The reaction of 5,5-dimethyl-1,3-cyclohexanedione (1) with ethyl acetoacetate (2) in CF_3CO_2H gives the 2-pyrone **4** and a xanthene-1,8-dione **5** instead of the reported 4-pyrone **3**. Sodium diethyl oxalacetate (**13**) and **1** react in a similar manner giving ester **14**, isomeric with ester **10** prepared by condensing **8** with ethyl oxalate. Acid **15**, prepared by hydrolysis of **14**, gives 2-pyrone **16** on decarboxylation, isomeric with 4-pyrone **9** prepared by condensation of **8** with ethyl formate. Ultraviolet spectra comparisons of **4**, **9**, and **16** substantiates the structure of **4**. Indan-1,3-dione (**6**) and **2** did not give a pyrone on condensation in CF_3CO_2H; instead, dimer **6a** is isolated.

Condensation of 5,5-dimethyl-1,3-cyclohexanedione (**1**) with ethyl acetoacetate (**2**) has been described[1] as

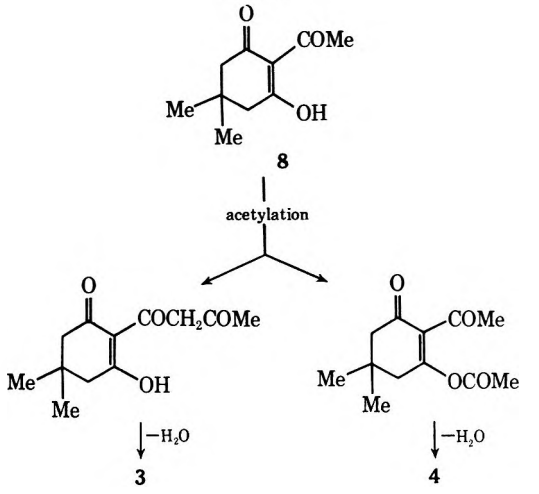


yielding 7,8-dihydro-2,7,7-trimethyl-4*H*-1-benzopyran-4,5(6*H*)-dione (**3**). We needed **3** for uv spectral comparison purposes and repeated the original preparation.[1] Instead of **3**, however, we isolated 7,8-dihydro-4,7,7-trimethyl-2*H*-1-benzopyran-2,5(6*H*)-dione (**4**) and 3,4,6,7-tetrahydro-3,3,6,6,9,9-hexamethylxanthene-1,8-(2*H*,5*H*)-dione (**5**).[2] The structure of **4** was substantiated by uv spectral correlations with several synthesized model 2- and 4-pyrones.

After considering the incongruities involved with the attempted preparation of **3**, we repeated the original preparation[1] involving the condensation of 1,3-indandione (**6**) and **2**. The nmr spectra indicated that none or only a very small amount of the proposed product **7** was present. Instead, we found that, when the reaction was worked up as described, mostly **6** was recovered, along with [$\Delta^{1,2'}$-biindan]-1′,3,3′-trione (**6a**)[3] and another high melting product. Apparently the original investigator's efforts resulted in the isolation of **6** and he described it as a new compound **7**. The originally described melting points (129 and 129–131°) agree with that reported for **6** (130–131°).[4] The originally reported found analysis (C, 73.70, 73.85; H, 3.94, 4.04),[1] presumably applicable to **7** ($C_{13}H_8O_3$), also agrees with that calculated for **6** ($C_9H_6O_2$) (C, 73.96; H, 4.14).

Efforts to provide a structural proof for **3** started with 2-acetyl-5,5-dimethyl-1,3-cyclohexanedione (**8**).[5] It became obvious that any acid- or base-catalyzed acetylation of **8**, followed by ring closure, could lead to the ambiguities shown in Scheme I. In fact, **4** was isolated from the neutral fraction separated from the preparation of **8**.

SCHEME I



Instead of synthesizing **3** or **4**, the problem was approached by preparing chromophorically identical 4- and 2-pyrones as uv spectral models. Two 4-pyrones easily prepared from **8** are 7,8-dihydro-7,7-dimethyl-4*H*-1-benzopyran-4,5(6*H*)-dione (**9**) and 5,6,7,8-tetrahydro-7,7-dimethyl-4,5-dioxo-4*H*-1-benzopyran-2-carboxylic acid ethyl ester (**10**). Compounds **9** and **10** were formed, respectively, by formylation and ethoxylation of the disodium salt of **8**, followed by dehydrative cyclization. The uv spectra of **9** and **10** (Table I) indicate that they have identical chromophores, but there is no similarity to the chromophore of **4**, which must be a 2-pyrone. Intermediate **11** was isolated and characterized en route to preparation of **9**.

(1) L. L. Woods, *J. Org. Chem.*, **34**, 2796 (1969).

(2) D. Vorländer and F. Kalkow, *Justus Liebigs Ann. Chem.*, **309**, 374 (1899); *Beilstein*, 17:509.

(3) W. Wislicenus, *Chem. Ber.*, **20**, 589 (1887).

(4) W. O. Teeters and R. L. Shriner, *J. Amer. Chem. Soc.*, **55**, 3026 (1933).

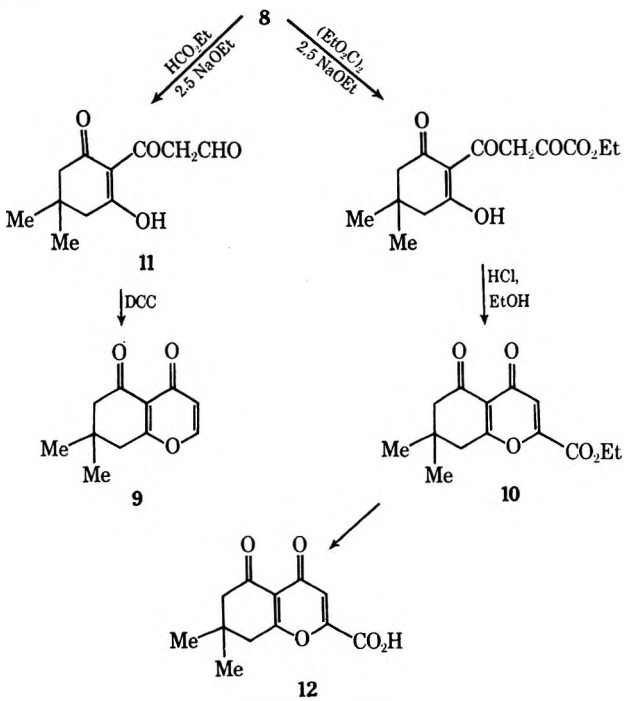
(5) W. Dieckmann and R. Stein, *Chem. Ber.*, **37**, 3370 (1904); A. W. Crossley and N. Renouf, *J. Chem. Soc.*, **101**, 1524 (1912).

TABLE I

ULTRAVIOLET SPECTRA IN 95% ALCOHOL

2-Pyrones		4-Pyrones	
Compd	mμ (ε)	Compd	mμ (ε)
4	262 (12,100), 290[a] (5960)	5	232 (15,450), 309 (5490)
14	263 (11,400), 296[a] (6530)	9	245 (8840)
15	263 (11,100), 296[a] (6240)	10	221 (22,800), 248 (7220)
15a	264 (10,250), 295[a] (5930)	12	217 (24,800), 247 (8830)
16	261 (12,230), 294[a] (6380)	12a	216 (28,800), 247 (10,160)

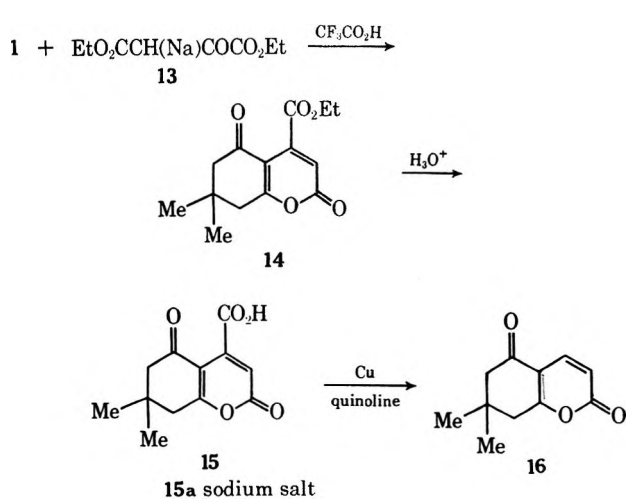
[a] Inflection points.



12a sodium salt

Ester **10** was hydrolyzed and characterized as the free acid **12** and sodium salt **12a**. Several attempts to decarboxylate **12** to **9** met only with extensive decomposition.

To complete the sequence, a series involving the 2-pyrones isomeric with **9**, **10**, and **12** was prepared. Condensation of **1** with sodium diethyl oxalacetate (**13**), using conditions similar to those described by



15a sodium salt

Woods,[1] gave a reasonable yield of 5,6,7,8-tetrahydro-7,7-dimethyl-2,5-dioxo-2*H*-1-benzopyran-4-carboxylic acid ethyl ester (**14**). Ester **14** is isomeric with **10**, and formation of a 2-pyrone (**14**) from **1** and **13** also illustrates a general trend to form 2-pyrones when 1,3 diketones and β-keto esters are condensed in an acid medium. Ester **14** was acid hydrolyzed, and the product was characterized as the free acid **15** and sodium salt **15a**. Acid **15** was easily decarboxylated with copper powder in refluxing quinoline to 7,8-dihydro-7,7-dimethyl-2*H*-1-benzopyran-2,5(6*H*)-dione (**16**), which is isomeric with **9**.

It is clearly evident from the uv data in Table I that **4** belongs to the 2-pyrone series. The spectral data in Table I also illustrate another point: that addition of a carboxyl or ethoxycarbonyl group to a 2- or 4-pyrone does not appreciably alter the electronic chromophore. By comparing the nmr spectra of **1**,[6] **4**, and **5** with that given by Woods[1] [solvent not reported, δ 1.10 (6), 1.66 (2), 2.20–2.80 (4), 3.35 (0.4), 5.50 (0.6)] for what he presumed to be **3**, it is evident that his condensation of **1** and **2** yielded only a mixture of **1** and **5**. The vinyl proton at δ 5.94 of **4** is not present in Woods mixture but the δ 5.50 vinyl of **1** and δ 1.66 methyls of **5** are.

Experimental Section

Melting points were taken in capillary tubes in an oil bath and are uncorrected. Solvents were removed *in vacuo* on a Büchi Rotavapor R. Anhydrous magnesium sulfate was used for all solution drying. Spectra were obtained under the supervision of Mr. Bruce Hofmann. The ir spectra were determined in KBr pellets using a Perkin-Elmer Model 21 spectrophotometer. The uv spectra were taken with a Perkin-Elmer Model 450 uv–visible NIR spectrophotometer. The nmr spectra were determined with a Varian Model A-60 or a Jeolco Model C-60HL nmr spectrometer using TMS in $CDCl_3$ and DMSO-d_6 and DSS in D_2O. Analyses were carried out on a Perkin-Elmer Model 240 elemental analyzer.

7,8-Dihydro-4,7,7-trimethyl-2*H*-1-benzopyran-2,5(6*H*)-dione (4) and 3,4,6,7-Tetrahydro-3,3,6,6,9,9-hexamethylxanthene-1,8-(2*H*,5*H*)-dione (5).—A solution of 70 g (0.5 mol) of **1** and 63.5 ml (0.5 mol) of **2** in 200 ml of CF_3CO_2H was refluxed for 22 hr. The solution was concentrated and the residue was poured into an Et_2O–H_2O mixture. An interphase was filtered off and crystallized (EtOH), giving 2.7 g of **5**: mp 249–252° (lit.[2] mp 245°); ir 6.04 (C=O), 6.20 μ (C=C); nmr ($CDCl_3$) δ 1.09 [s, 12, $CH_2C(CH_3)_2CH_2$], 1.66 [s, 6, C=CC$(CH_3)_2$C=C], 2.27 (s, 4, CH_2CO), 2.35 [s, 4, C=C(O)CH_2].

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.48; H, 8.67.

The Et_2O–H_2O filtrate of **5** was separated and the Et_2O was washed successively with H_2O (twice), saturated $NaHCO_3$ (until basic), cold 1 *N* NaOH (twice with 300 ml), H_2O, and cold dilute HCl. After the washings, additional **5** (4.5 g, mp 244–247°) was filtered off. The Et_2O in the filtrate was washed with brine, dried, and concentrated, giving 18 g of a yellow solid, mp 105–135°, consisting of a mixture of **4** and **5**. The mixture was crystallized (EtOH), giving 7.7 g of a white solid, mp 110–210°, consisting of a 6:1 mixture of **4** and **5**. An attempt to separate the mixture on Woelm grade III neutral alumina failed, but, when 2.0 g of the mixture was sublimed at 110 ± 5° (0.05 mm) in a Nester–

(6) Varian Spectra Catalog, Vol. 2, Spectra No. 512: nmr ($CDCl_3$) δ 1.06 [s, $C(CH_3)_2$, keto form], 1.09 [s, $C(CH_3)_2$, enol form], 2.29 [s, $C(CH_3)_2$-CH_2CO, enol and keto form], 2.56 [s, $CH_3C(OH)$=CH], 3.36 (s, $COCH_2CO$), 5.51 [s, C(OH)=CHCO], 10.90 (s, OH).

Faust Model NFS-60 sublimer, 1.65 g of **4**, mp 108–112°, collected in the cooled cone and was crystallized (EtOH), giving white crystals: mp 108–111°; ir 5.77 and 6.00 (C=O), 6.17 and 6.45 μ (C=C); nmr ($CDCl_3$) δ 1.14 [s, 6, $C(CH_3)_2$], 2.45 (s, 3, $CH=CCH_3$), 2.48 (s, 2, CH_2CO),[7] 2.78 [s, 2, $C=C(O)CH_2$], 5.94 (s, 1, vinyl).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.68; H, 6.96.

An additional 0.4 g of **5**, mp 248–250°, collected on the outer shell of the sublimer above the oil level. An attempt to repeat this separation on a larger scale failed.

Condensation of 2 with 6 in Refluxing CF_3CO_2H.—A solution of 12.6 ml (0.10 mol) of **2** and 14.6 g (0.10 mol) of **6** in 40 ml of CF_3CO_2H was refluxed for 2 hr and the resulting mixture was poured into 400 ml of H_2O. Filtration gave 12 g of a brown solid, which was triturated three times with 400 ml of boiling hexane. Concentration of the hexane gave 6.3 g of a yellow solid, which was sublimed at 100° (0.05 mm), giving 5.8 g of **6**, mp 128–130°, mmp 128–130° with authentic **6**. The hexane-insoluble solid was triturated three times with 200 ml of boiling EtOAc. Concentration of the EtOAc gave 2.3 g of **6a** as a tan solid, mp 173–183°. The solid was recrystallized from C_6H_5Me, giving yellow crystals of **6a**: mp 205–208° (lit.[3] mp 206–208°); ir[8] 5.82, 5.93, and 6.20 (C=O), 6.35 μ (C=C); uv max (95% EtOH) 245 mμ (ε 24,100), 340 (20,300); nmr ($CDCl_3$) δ 4.15 (s, 2, CH_2), 7.60–8.40 (m, 7, aromatic), 9.50–9.78 (m, 1, aromatic).

Anal. Calcd for $C_{18}H_{10}O_3$: C, 78.82; H, 3.68. Found: C, 79.10; H, 3.87.

The remaining 3 g of solid melted above 300° and was very insoluble in DMSO, making it difficult to get a good nmr: ir 5.83, 5.95, 6.20, and 6.37 μ.

5,6,7,8-Tetrahydro-7,7-dimethyl-4,5-dioxo-4*H*-1-benzopyran-2-carboxylic acid Ethyl Ester (10).—Absolute EtOH (10.25 ml, 0.175 mol) was added to a mixture of 6.24 g (0.13 mol) of 50% NaH in 250 ml of C_6H_5Me. A solution of 9.11 g (0.050 mol) of **8** in 34 ml (0.25 mol) of $(EtO_2C)_2$ was added to the C_6H_5Me mixture at 10–20° over 20 min. The resulting mixture was stirred at 50° for 3 hr and poured into 500 ml of ice–water. The water solution was washed twice with Et_2O and acidified to pH 1 at 0–10° with concentrated HCl in the presence of Et_2O. The water layer was extracted twice with Et_2O. The ether was washed with brine, dried, and concentrated, giving 16.1 g of an amber oil. The oil was chromatographed on 160 g of Florex AA-RVM 60–90 mesh in C_6H_6. Two 500-ml fractions of C_6H_6, followed by two of $CHCl_3$, were collected. The first $CHCl_3$ fraction was concentrated, giving 1.5 g (11%) of **10**, mp 128–132°. After crystallization from ethyl acetate–hexane, the product had mp 134–137°; ir 5.74, 5.86, and 6.06 (C=O), 6.34 μ (C=C); nmr ($CDCl_3$) δ 1.16 [s, 6, $C(CH_3)_2$], 1.41 (t, 3, J = 7.2 Hz, CH_3), 2.46 (s, 2, 6-CH_2),[7] 2.90 (s, 2, 8-CH_2), 4.47 (q, 2, J = 7.2 Hz, CH_2CH_3), 7.10 (s, 1, vinyl).

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.56; H, 6.05.

Concentration of the first C_6H_6 fraction gave 8.0 g of a light yellow solid, mp 48–90°. The solid was dissolved in 50 ml of absolute EtOH, 3 ml of EtOH saturated with HCl gas was added, and the solution was refluxed for 20 min and cooled in ice, giving 3.5 g of light pink crystals of **10**, mp 130–136°.

5,6,7,8-Tetrahydro-7,7-dimethyl-4,5-dioxo-4*H*-1-benzopyran-2-carboxylic Acid (12) and Its Sodium Salt (12a).—A solution of 20.0 g (0.076 mol) of **10** in 240 ml of 1:1 dioxane–concentrated hydrochloric acid was refluxed for 3 hr and kept overnight at room temperature. Water (250 ml) was added and the mixture was cooled to 0–5°, giving 11.7 g of **12**. The crude product was crystallized (MeCN), giving 8.7 g (49%) of **12** as white crystals: mp 210–212° dec; ir 5.73, 5.92, and 6.09 (C=O), 6.30 and 6.45 μ (C=C); nmr (DMSO-d_6) δ 1.08 [s, 6, $C(CH_3)_2$], 2.36 (s, 2, 6-CH_2), 2.89 (s, 2, 8-CH_2), 6.80 (s, 1, vinyl), 10.20 (s, 1, CO_2H).

Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 60.97; H, 5.12.

To a boiling, analytically filtered solution of 2.64 g (0.010 mol) of **10** in 50 ml of absolute EtOH was added, with stirring over 1 min, 1.9 ml of 5.25 *N* NaOH. Crystals formed rapidly and the mixture was kept on a steam bath for 10 min, cooled in ice, and filtered, giving 1.7 g (66%) of **12a** as yellow crystals: mp >300°; ir 5.90 and 6.13 (C=O), 6.42 μ (C=C); nmr (D_2O) δ 1.15 [s, 6, $C(CH_3)_2$], 2.56 (s, 2, 6-CH_2), 3.04 (s, 2, 8-CH_2), 6.96 (s, 1, vinyl).

Anal. Calcd for $C_{12}H_{11}NaO_5$: C, 55.82; H, 4.30. Found: C, 55.65; H, 4.45.

2-(Formylacetyl)-5,5-dimethyl-1,3-cyclohexanedione (11).—**11** was prepared in the same manner as **10**, but 20.2 ml (0.25 mol) of EtO_2CH was used instead of $(EtO_2C)_2$ and the Na salt of **11** was filtered off after the 3-hr heating period. An aqueous (300 ml) solution of the salt was washed with Et_2O and acidified to pH 1 with concentrated HCl in the presence of Et_2O. After 10 min of stirring, 5.7 g (54%) of **11**, mp 131° dec, was filtered off and crystallized (ethyl acetate–hexane), affording 4.4 g (42%) of **11** as yellow crystals: mp 135–136.5° dec; ir 6.2 (C=O), 6.62 μ (C=C); uv max (95% EtOH) 249 mμ (center of broad plateau) (ε 8380), 335 (9300); nmr (DMSO-d_6) δ 1.00 [s, $C(CH_3)_2$], 2.40 (s, CH_2), 7.04 (d, J = 12 Hz, vinyl), 8.04 (d, J = 12 Hz, vinyl), the ratios being unobtainable because of the DMSO-d_5 interference with the CH_2 peaks.

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.74; H, 6.81.

7,8-Dihydro-7,7-dimethyl-4*H*-1-benzopyran-4,5(6*H*)-dione (9).—DCC (1.073 g, 0.0052 mol) was added to a warm solution of 1.074 g (0.00511 mol) of **11** in 20 ml of THF. After 20 hr at room temperature, the red mixture was filtered and the cake (1.0 g) was washed with THF. The filtrate was concentrated and the red residue was triturated twice with boiling Et_2O, leaving 0.36 g of a red solid. The ether was treated with charcoal and concentrated, giving 0.610 g of a gummy solid, which was chromatographed on activity I silica gel in EtOAc. Elution with 150 ml EtOAc removed the DCC. Collection of fractions with increasing amounts of MeCOMe to 100% and subsequent concentration afforded 0.30 g (31%) of **9**. Crystallization from chloroform–hexane yielded a product with mp 115–117.5°; ir 5.89 and 6.07 (C=O), 6.42 μ (C=C); nmr ($CDCl_3$) δ 1.15 [s, 6, $C(CH_3)_2$], 2.43 (s, 2, 6-CH_2), 2.77 (s, 2, 8-CH_2), 6.38 (d, 1, J = 6 Hz, vinyl), 7.72 (d, 1, J = 6 Hz, vinyl).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: 68.44; H, 6.54.

5,6,7,8-Tetrahydro-7,7-dimethyl-2,5-dioxo-2*H*-1-benzopyran-4-carboxylic Acid Ethyl Ester (14).—A mixture of 14.0 g (0.1 mol) of **1** and 21.0 g (0.1 mol) of **13** was refluxed in 50 ml of CF_3CO_2H for 4 hr and then stirred overnight at room temperature. After concentration, the residue was poured into an Et_2O–H_2O mixture. The Et_2O was washed successively with saturated $NaHCO_3$ (until basic), cold 0.5 *N* NaOH, dilute HCl, H_2O, and brine. It was then dried and concentrated, giving 7.4 g (28%) of **14** as a white solid. Crystallization (ethyl acetate–hexane) gave 5.6 g of white crystals: mp 136–138°; ir 5.74 and 5.96 (C=O), 6.16 and 6.43 (C=C); nmr ($CDCl_3$) δ 1.18 [s, 6, $C(CH_3)_2$], 1.38 (t, 3, J = 7.5 Hz, CH_3), 2.48 (s, 2, 6-CH_2), 2.80 (s, 2, 8-CH_2), 4.46 (q, 2, J = 7.5 Hz, CH_2CH_3), 6.25 (s, 1, vinyl).

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.59; H, 6.01.

5,6,7,8-Tetrahydro-7,7-dimethyl-2,5-dioxo-2*H*-1-benzopyran-4-carboxylic Acid (15) and Its Sodium Salt (15a).—A solution of 10 g (0.038 mol) of **14** in 100 ml of 1:1 dioxane–20% hydrochloric acid was refluxed for 6 hr and kept at room temperature overnight. Filtration gave 8.0 g (89%) of **15**, mp 218–223° dec. The crude product was crystallized (EtOH), giving 6.4 g of **15** as white crystals: mp 222–224° dec; ir 5.65, 5.77, and 6.15 (C=O), 6.45 μ (C=C); nmr (DMSO-d_6) δ 1.11 [s, 6, $C(CH_3)_2$], 2.48 (s, 2, 6-CH_2), 2.87 (s, 2, 8-CH_2), 6.39 (s, 1, vinyl).

Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 60.78; H, 5.35.

To a boiling, analytically filtered solution of 2.1 g (0.0089 mol) of **15** in 75 ml of absolute EtOH was added 3.3 ml of 2.74 *N* sodium 2-ethylhexanoate in 1-butanol. The mixture was cooled, giving 1.3 g (58%) of **15a** as white crystals: mp >300°; ir 5.66, 5.72, 5.95, and 6.20 (C=O), 6.48 μ (C=C); nmr (D_2O) δ 1.10 [s, 6, $C(CH_3)_2$], 2.53 (s, 2, 6-CH_2), 2.89 (s, 2, 8-CH_2), 6.13 (s, 1, vinyl).

Anal. Calcd for $C_{12}H_{11}NaO_5$: C, 55.82; H, 4.30. Found: C, 55.88; H, 4.40.

7,8-Dihydro-7,7-dimethyl-2*H*-1-benzopyran-2,5(6*H*)-dione (16).—A stirred mixture of 5.0 g (0.021 mol) of **15**, 0.98 g of Cu powder, and 10 ml of quinoline was placed in an oil bath at 250°. Decarboxylation was essentially complete after 10 min, and the

(7) Routine assignment of the higher field methylene to the 6 position on the 1-benzopyran nucleus is based on data in Varian Spectra Catalog, Spectra No. 512.

(8) Spectrum identical with that found in the Sadtler Index (Spectra No. 18437).

mixture was cooled and filtered. An Et_2O solution of the filtrate was washed successively with 1 *N* HCl (five times), saturated $NaHCO_3$, H_2O, and brine. It was then dried and concentrated, giving 2.33 g of a yellow solid, mp 79–87°. The solid was recrystallized from hexane and cyclohexane, giving 1.66 g (41%) of **16** as light yellow crystals: mp 89–92°; ir 5.76 and 5.96 (C=O), 6.14 and 6.40 μ (C=C); nmr ($CDCl_3$) δ 1.16 [s, 6, $C(CH_3)_2$], 2.46 (s, 2, 6-CH_2), 2.79 (s, 2, 8-CH_2), 6.30 (d, 1, J = 9.75 Hz, vinyl), 7.91 (d, 1, J = 9.75 Hz, vinyl).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.31; H, 6.39.

Registry No.—**3**, 20452-84-0; **4**, 3265-69-8; **5**, 33777-60-5; **6**, 606-23-5; **6a**, 1707-95-5; **7**, 20452-88-4; **9**, 33777-64-9; **10**, 33777-65-0; **11**, 33777-66-1; **12**, 33777-67-2; **12a**, 33777-68-3; **14**, 33886-29-2; **15**, 33777-69-4; **15a**, 33777-70-7; **16**, 33777-71-8; trifluoroacetic acid, 76-05-1.

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α- and β-(Trifluoromethylthio)acrylic Acid Derivatives

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The product of the free-radical addition of CF_3SCl to methyl acrylate has been converted to a series of α-CF_3S-acrylic acid derivatives. The preparation of the corresponding β-CF_3S-substituted compounds began with the addition of CF_3SH to methyl propiolate. (Trifluoromethylthio)acetonitrile readily undergoes Knoevenagel reactions to yield α-CF_3S-substituted acrylonitriles.

Following the development of convenient laboratory syntheses for bis(trifluoromethylthio)mercury, trifluoromethanethiol, and trifluoromethanesulfenyl chloride, a modest number of CF_3S-substituted organic compounds have been synthesized.[1] To date no CF_3S-substituted, unsaturated acids or derivatives have been reported. This paper summarizes the results of a study of methods of preparation and the properties of CF_3S-substituted acrylic acid derivatives.

Results and Discussion

α-CF_3S-Substituted Acrylic Acid Derivatives.—For preparation of several α-CF_3S-substituted acrylic acid derivatives, the free-radical addition of trifluoromethanesulfenyl chloride (CF_3SCl) to methyl acrylate served as the starting point. When carried out with a large excess of CF_3SCl, the reaction yielded as the major product a 1:1 adduct fraction which contained about 90% methyl α-(trifluoromethylthio)-β-chloropropionate (**1**) and 10% of an isomeric material, presumably the other possible 1:1 adduct (**2**) (eq 1).

$$CF_3SCl + CH_2{=}CHCO_2CH_3 \xrightarrow{h\nu} \underset{\mathbf{1}}{ClCH_2\overset{CF_3S}{\overset{|}{C}}HCO_2CH_3} + \underset{\mathbf{2}}{CF_3SCH_2\overset{Cl}{\overset{|}{C}}HCO_2CH_3} + \underset{\mathbf{3}}{ClCH_2\overset{CO_2CH_3}{\overset{|}{C}}HCH_2\overset{SCF_3}{\overset{|}{C}}HCO_2CH_3} \quad (1)$$

A considerable quantity of a 2:1 adduct (**3**) was formed, which, according to gas chromatography and ^{19}F nmr spectroscopy, contained two isomers in roughly equal amounts.

The orientation of the major 1:1 adduct (**1**) was established by analysis of the ^{13}C nmr pattern.[2,3] The ^{13}C resonances of the hydrogen-bearing carbons along with the ^{13}C–H coupling constants are shown in Table I.

TABLE I

^{13}C NMR SPECTRUM OF METHYL α-(TRIFLUOROMETHYLTHIO)-β-CHLOROPROPIONATE (NEAT)

$$ClCH_2\overset{SCF_3}{\overset{|}{C}}HCO_2CH_3$$

Carbon atom	Chemical shift, ppm	Splitting pattern	J (^{13}C–H), Hz
CH_3	73.4	Quartet	149
CH	68.2	Doublet	148
CH_2	63.5	Triplet	158

Neither of the resonances for the carbons possibly containing the CF_3S group showed any spin–spin coupling clearly attributable to the presence of this group, and thus no structure assignment could be made on that basis. However, since values of J (^{13}C–H) for CH groups with chlorine substituents have been observed to be 150 Hz and higher,[4] it is concluded that the CH group, with J (^{13}C–H) of 148 Hz, cannot have the Cl, but must instead have the CF_3S group as substituent. This structure is consistent with the structures of the dehydrochlorination products from the 1:1 adduct discussed below.

Structure **3** was assigned to the 2:1 adduct on the basis of a dehydrochlorination experiment (eq 2), which produced a single, unsaturated ester in 78.5% yield (distilled). On the basis of the ^1H nmr and infrared spectra, **4** is the most likely structure for this product. The ^1H nmr pattern contains two unsplit CH_3 resonances, a CH_2 resonance split to a doublet, each com-

(1) J. F. Harris, Jr., *J. Org. Chem.*, **32**, 2063 (1967).

(2) Neither the ^1H nor the ^{19}F nmr pattern of the mixture of 1:1 adducts gave evidence sufficient for structure assignment.

(3) The author is indebted to Dr. G. S. Reddy of this laboratory for determination and interpretation of the ^{13}C nmr pattern of the 1:1 adduct fraction.

(4) For example, see J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, New York, N. Y., 1965, p 195, Table 5.21.

TABLE II

^{1}H AND ^{19}F NMR SPECTRA OF CF_3S-ACRYLIC ACID DERIVATIVES

Compd	^{1}H, δ (ppm) from the ^{1}H resonance of $(CH_3)_4Si$			^{19}F, δ (ppm) from the ^{19}F resonance of Cl_3CF
	=CH	CH_3	Other	
CH_3O_2C SCF_3 $CH_2=C-CH_2CHCO_2CH_3$ **4**	6.29 (2) J_{H-H} = 1.2 Hz 5.73 (2, 3) J_{H-H} = 1.2 Hz J_{H-H} = 1.0 Hz	3.73 (1) 3.77 (1)	2.89 (CH_2, 2 br) J_{H-H} = 7.8 Hz 4.12 (CH, 3) J_{H-H} = 7.8 Hz	−41.2 (1)
H_B SCF_3 $C=C$ H_A CO_2CH_3 **5**	6.86[a] (4) J_{H-F} = 0.9 Hz 6.32 (4) J_{H-F} = 0.8 Hz J_{H-H} = 0	3.81 (1)		−42.8 (2, 2) J = 0.8 Hz
H_B SCF_3 $C=C$ H_A CO_2H **6**	7.15 (1 broad) 6.61 (1 broad)		11.8 (OH, 1)	−42.6 (3) J = <1 Hz
H SCF_3 $C=C$ H CN **9**	6.73 (5) J_{H-H} = ~0.7 Hz 6.60			−49.4 (2, 2) J = 0.8 Hz J = 0.4–0.5 Hz
CF_3S CO_2CH_3 $C=C$ H H **11a**	7.17 (2 broad) J_{H-H} = 10 Hz 6.10 (2, 4) J_{H-F} = 1 Hz	3.76 (1)		−45.9 (2, 2) J = 1 Hz J = 0.4 Hz
CF_3S H $C=C$ H CO_2CH_3 **11b**	7.53 (2) J_{H-H} = 15.6 Hz 6.09 (2, 4) J_{H-F} = 0.7 Hz	3.71 (1)		−42.4 (2) J = 0.7 Hz
CF_3S CN $C=C$ H H **15a**	7.27 (2) J_{H-H} = 10.2 Hz 5.76 (2, 4) J_{H-F} = 1.1 Hz			−42.1 (2) J = 1.1 Hz
CF_3S H $C=C$ H CN **15b**	7.36 (2) J_{H-H} = 16.1 Hz 5.69 (2, 4) J_{H-F} = 0.6 Hz			−42.2 (2) J = 0.6 Hz

[a] Analysis of this spectrum based on the spectra of $CF_3SCH=CH_2$ (ref 1) and methyl acrylate by the method of E. U. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell [*Tetrahedron*, 25, 691 (1969)] suggests that the low-field resonance belongs to the proton cis to the carbomethoxy group, *i.e.*, H_A.

$$\underset{\textbf{3}}{H_3CO_2C\ SCF_3\ ClCH_2CHCH_2CHCO_2CH_3} + (C_2H_5)_3N \xrightarrow{THF} \underset{\textbf{4}}{H_3CO_2C\ SCF_3\ CH_2=CCH_2CHCO_2CH_3} \quad (2)$$

ponent of which is rather broad, a CH resonance (doublet), and two vinyl proton resonances (Table II). These vinyl protons are mutually spin coupled (J = 1.2 Hz), and the high-field one is, in addition, split to triplets, thus indicating the proximity of the CH_2 group. This pattern supports structure **4** and makes alternative structures in which the CH_2 group is not adjacent to the double bond unlikely. The logical precursor to **4** is **3**, whose two asymmetric centers account for the two components indicated by gas chromatography and ^{19}F nmr spectroscopy.

The orientation of the major 1:1 and 2:1 adducts just discussed suggests that the principal adding species in the radical-chain addition of CF_3SCl to methyl acrylate is the chlorine atom which adds to the CH_2 carbon, the usual site of radical attack in methyl acrylate. The resulting radical apparently either chain transfers by attacking the sulfur atom of the sulfenyl chloride to give the major 1:1 adduct obtained, or else adds to another molecule of methyl acrylate to produce a radical which leads by chain transfer to the 2:1 adduct. The main steps assumed in this process are shown in eq 3–7.

$$CF_3SCl \xrightarrow{h\nu} CF_3S\cdot + Cl\cdot \quad (3)$$

$$Cl\cdot + CH_2=CHCO_2CH_3 \longrightarrow ClCH_2\dot{C}HCO_2CH_3 \quad (4)$$

$$ClCH_2\dot{C}HCO_2CH_3 + CF_3SCl \longrightarrow \underset{}{CF_3S\ ClCH_2CHCO_2CH_3} + Cl\cdot \quad (5)$$

$$ClCH_2\dot{C}HCO_2CH_3 + CH_2=CHCO_2CH_3 \longrightarrow \underset{}{H_3CO_2C\ CO_2CH_3\ ClCH_2CHCH_2\dot{C}H\cdot} \quad (6)$$

$$\underset{}{H_3CO_2C\ CO_2CH_3\ ClCH_2CHCH_2\dot{C}H\cdot} + CF_3SCl \longrightarrow \underset{}{H_3CO_2C\ CO_2CH_3\ ClCH_2CHCH_2CHSCF_3} + Cl\cdot \quad (7)$$

This reaction is wholly analogous to previously studied examples of free-radical additions of CF_3SCl to unsymmetrical double bonds.[5]

Dehydrochlorination of the 1:1 adduct fraction was easily achieved by treatment with triethylamine in anhydrous ether, and methyl α-(trifluoromethylthio)-acrylate (**5**) was obtained in over 60% yield (eq 8). The proof of structure for **5** is based primarily upon spectral evidence. Thus the ^{1}H nmr pattern (Table II)

(5) J. F. Harris, Jr., *J. Amer. Chem. Soc.*, **84**, 3148 (1962).

$$ClCH_2\underset{|}{\overset{CF_3S}{C}}HCO_2CH_3 + (C_2H_5)_3N \longrightarrow \underset{5}{CH_2{=}\overset{CF_3S}{\overset{|}{C}}CO_2CH_3} \quad (8)$$

indicates two vinyl protons each spin coupled to the CF_3 group by 8–9 Hz but apparently not coupled to one another, consistent with their being on the same carbon atom. This pattern is clearly different from those of the isomeric *cis*- and *trans*-methyl β-(trifluoromethylthio)acrylates discussed later in this paper. Further support for structure **5** is seen in the infrared spectrum, which contains a =CH stretch band at 3106 cm^{-1} in the region consistent for a $R_2C{=}CH_2$ type structure.[6] The C=C stretch band occurs at 1603 cm^{-1}. After several days at room temperature, **5** polymerized to a solid polymer.

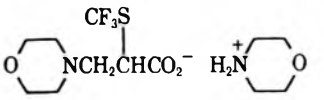
Treatment of the CF_3SCl–methyl acrylate 1:1 adduct fraction with dilute aqueous HCl at reflux also resulted in dehydrochlorination, giving a small amount of **5**, α-(trifluoromethylthio)acrylic acid (**6**) (32%), and a high-boiling fraction containing (trifluoromethylthio)-hydroxypropionic acid (**7**) (eq 9). The vinyl proton

$$ClCH_2\underset{|}{\overset{CF_3S}{C}}HCO_2CH_3 + H_2O \xrightarrow{HCl} \underset{5}{CH_2{=}\overset{CF_3S}{\overset{|}{C}}CO_2CH_3} + \underset{6}{CH_2{=}\overset{CF_3S}{\overset{|}{C}}CO_2H} + \underset{7}{HOCH_2\overset{CF_3S}{\overset{|}{C}}HCO_2H} \quad (9)$$

portion of the ^1H nmr spectrum of the acid **6** (Table II) is similar to that of the ester **5** and indicates that the product is indeed the α-CF_3S acid. On the basis of elemental analysis and the infrared spectrum, it was concluded that the high-boiling fraction is a CF_3S-substituted hydroxypropionic acid. The infrared spectrum contains a broad band in the 3330 cm^{-1} region (OH), a broad band at 2632 cm^{-1} (acid OH), bands at 2967 and 2899 cm^{-1} (saturated CH), and a carbonyl band at 1733 cm^{-1} as well as bands in the 1110–1250 cm^{-1} region (CF). There was no indication of carbon–carbon unsaturation. The ^{19}F nmr spectrum contains two resonances in a ratio of 85:15, thus indicating the presence of two CF_3S-containing compounds in the fraction. The 85% peak is unsplit and is no help in structure assignment. The 15% peak is split to a triplet (J = 0.7 Hz), suggesting that the minor component is probably α-hydroxy-β-(trifluoromethylthio)-propionic acid. The major component is thus presumed to be β-hydroxy-α-(trifluoromethylthio)propionic acid (**7**), although admittedly other isomeric structures are possible.

It is not clear from the experiment just described whether the hydroxy acids arise from a substitution reaction on the saturated ester (or acid), or whether there is first a dehydrochlorination followed by addition of the elements of water. Addition of water to the double bond was observed in an experiment in which the ester **5** was heated with dilute HCl giving the unsaturated acid **6** and the hydroxy acid **7** as major products. Another addition to the double bond occurred when the acid **6** was treated with excess morpholine. Although not proved, the structure of the product, isolated as the morpholine salt, was assumed to be **8**.

(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 34.



8

Application of the traditional sequence for converting acids to nitriles gave very small amounts of α-(trifluoromethylthio)acrylonitrile (**9**) (eq 10).

$$CH_2{=}\overset{SCF_3}{\overset{|}{C}}CO_2H \xrightarrow[3.\ P_2O_5]{1.\ SOCl_2\ 2.\ NH_3} \underset{9}{CH_2{=}\overset{SCF_3}{\overset{|}{C}}CN} \quad (10)$$

Somewhat higher yields were obtained from a two-step process starting with acrylamide and CF_3SCl (eq 11). The structure assigned to this nitrile (**9**) is

$$CF_3SCl + CH_2{=}CH\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow{\text{acetonitrile}} [ClCH_2\overset{SCF_3}{\overset{|}{C}}HCONH_2] \xrightarrow{P_2O_5} \underset{9}{CH_2{=}\overset{SCF_3}{\overset{|}{C}}CN} \quad (11)$$

based primarily upon the similarity of the vinyl proton portion of the ^1H nmr pattern to that of the other compounds in the α-CF_3S series (Table II).

Another entry into the synthesis of α-CF_3S-substituted acrylonitrile derivatives is *via* Knoevenagel reactions of aldehydes and ketones with (trifluoromethylthio)acetonitrile (**10**) (prepared according to eq 12). The reaction appears to be rather general, and

$$CF_3SCl + CH_2{=}C{=}O \longrightarrow CF_3SCH_2\overset{O}{\overset{\|}{C}}Cl \xrightarrow[2.\ P_2O_5]{1.\ NH_3} \underset{10}{CF_3SCH_2CN} \quad (12)$$

examples were carried out with aldehydes and ketones containing both aromatic and aliphatic substituents (eq 13) (Tables III–V).[7]

$$R(R')C{=}O + CF_3SCH_2CN \longrightarrow R(R')C{=}C\begin{matrix}SCF_3\\ \diagdown\\ \diagup\\ CN\end{matrix} \quad (13)$$

As with other Knoevenagel reactions, those examples with hydrocarbon aromatic aldehydes were most rapid and went in highest yield.[8] In the reactions with aliphatic ketones and pentafluorobenzaldehyde,[9] relatively large amounts of catalyst were used in order to achieve substantial reactions. In all cases, the expected α-CF_3S acrylonitrile was obtained as the major product, but sometimes minor yields of higher boiling, unidentified compounds were also noted (Table III). The elemental analyses and infrared, ^1H, and ^{19}F nmr spectra from all of the major products were consistent with the assigned acrylonitrile structure (Tables IV and V). In those reactions with unsymmetrical carbonyl compounds, both the cis and trans isomers of the ex-

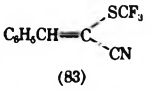
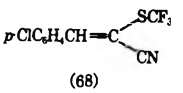
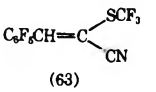
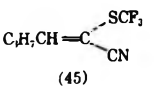
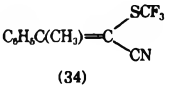
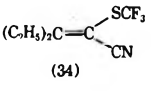
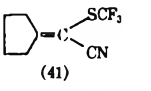
(7) Knoevenagel reactions involving sulfonyl-substituted acetonitriles and aryl- or alkylthioacetic acids and -acetamides as the active methylene component are well known, but the reactions reported in this paper are apparently the first employing an acetonitrile with a thiyl substituent: G. Jones, "The Knoevenagel Reaction," in "Organic Reactions," Vol. 15, Wiley, New York, N. Y., 1967.

(8) G. Jones, "The Knoevenagel Reaction," in "Organic Reactions," Vol. 15, Wiley, New York, N. Y., 1967.

(9) The lower reactivity of pentafluorobenzaldehyde compared with benzaldehyde in Knoevenagel reactions has been noted previously: N. G. Ivanova, V. A. Barkhash, and N. N. Vorozhtsov, *J. Gen. Chem. USSR*, **39**, 1317 (1969).

TABLE III

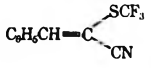
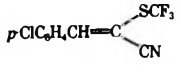
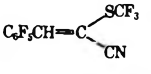
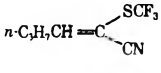
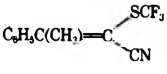
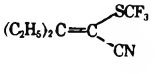
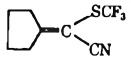
KNOEVENAGEL REACTIONS OF ALDEHYDES AND KETONES WITH CF_3SCH_2CN

Aldehyde or ketone, g (mol)	CF_3SCH_2CN, g (mol)	Piperidine, ml	Benzene, ml	Reflux time, hr	Product (yield of distilled product, %)	Comments
C_6H_5CHO 16.0 (0.151)	20 (0.142)	3	145	1/2	 (83)	The ^{19}F nmr spectrum of crude product indicated two isomers in a ratio of 90.1:8.6.
p-ClC_6H_4CHO 20 (0.142)	20 (0.142)	3	145	1 1/2	 (68)	
C_6F_5CHO 17 (0.0866)	10 (0.0707)	5[a]	70	7 2/3	 (63)	The ^{19}F nmr spectrum of the distilled product indicated two isomers in a ratio of 79:21.
n-C_3H_7CHO 6 (0.0831)	10 (0.0707)	1.5	70	2	 (45)	Gc before distillation showed 83.9% expected product (two isomers — ratio 71:29) and 16.1% of higher retention time materials.
$C_6H_5C(=O)CH_3$ 9.1 (0.0757)	10 (0.0707)	5.5[a]	70	25 1/4	 (34)	Gc before distillation indicated two isomers in a ratio of 41:59.
$C_2H_5C(=O)C_2H_5$ 10 (0.116)	10 (0.0707)	5.0[a]	70	22 1/2	 (34)	Gc before distillation showed 76.8% expected product plus two other materials.
 10 (0.119)	10 (0.0707)	1.5	70	21 1/3	 (41)	Gc before distillation showed 91% expected product plus 9% of an unknown material at longer retention time.

[a] Addition of an initial 1.5 ml of piperidine resulted in the separation of very little water after 1 hr or more of reflux. Additional piperidine was added, usually in 1.5-ml increments, until the totals shown were obtained.

TABLE IV

PRODUCTS FROM KNOEVENAGEL REACTIONS OF CF_3SCH_2CN

Structure	Registry no.	Bp, °C (mm)	Molecular formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Fluorine, % Calcd	Fluorine, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Sulfur, % Calcd	Sulfur, % Found
	7437-06-0	69 (0.15)	$C_{10}H_6F_3NS$					24.9	25.1			14.0	13.6
	7437-05-9	102 (0.4) 108 (0.5)	$C_{10}H_5ClF_3NS$							5.3	5.7	12.2	12.4
	34033-90-4	67–71 (0.1)	$C_{10}HF_8NS$	37.6	38.2 38.0	0.3	0.7 0.5	47.6	47.0 47.4			10.0	10.3 10.1
	34033-91-3	69–80 (16)	$C_7H_5F_3NS$	43.1	43.3 43.1	4.1	4.3 4.3	29.2	29.1 29.1			16.4	16.8 16.8
	34033-92-6	81 (0.2) 94 (0.45)	$C_{11}H_8F_3NS$	54.3	54.3 54.1	3.3	3.7 3.8	23.4	23.5 23.3				
	34033-93-7	61 (1.75)	$C_8H_{10}F_3NS$	46.0	45.8 45.5	4.8	4.9 4.7					15.3	15.6 15.7
	4033-94-8	40 (0.025)	$C_8H_8F_3NS$	46.4	46.4 46.5	3.9	4.2 4.0	27.5	26.8 27.0				

pected products were detected by gas chromatography and the nmr spectra, but in no case could a specific assignment be made on the basis of the spectra obtained. The proportion of the two isomers varied from 91:9 with benzaldehyde to 41:59 with acetophenone.

β-CF_3S-Substituted Acrylic Acid Derivatives.—A route to β-CF_3S acrylic acid derivatives was provided by the uv-catalyzed addition of CF_3SH to methyl propiolate, which yielded methyl β-(trifluoromethylthio)acrylate (**11**) in over 50% yield (eq 14). This process gave both the cis and trans isomers (ratio 77.5:22.5), which were isolated by preparative-scale

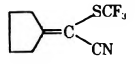
$$CF_3SH + HC{\equiv}CCO_2CH_3 \xrightarrow{h\nu} \underset{\mathbf{11}}{CF_3SCH{=}CHCO_2CH_3} \quad (14)$$

gas chromatography. Structures were assigned on the basis of the ^1H nmr spectra, each of which contained in addition to a CH_3 resonance two coupled vinyl proton resonances: J = 10 (77.5% isomer) and 15.6 Hz (22.5% isomer). Since trans H–H coupling is almost always greater than cis H–H coupling[10] in such struc-

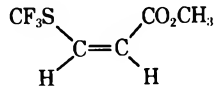
(10) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, p 238.

TABLE V

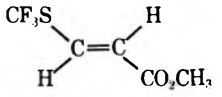
SPECTRAL CHARACTERIZATION OF PRODUCTS FROM KNOEVENAGEL REACTIONS OF CF_3SCH_2CN

Compd	Infrared, cm^{-1}	^1H nmr (ppm from TMSI)	^{19}F nmr (ppm from ^{19}F resonance of Cl_3CF)
$C_6H_5CH=C(SCF_3)(CN)$	1592, 1570, 1531, 1499 (C=C) 3058 and 3096 (=CH) 2222 (-C≡N) 1105 and 762 ($-SCF_3$) 688 and 742 (monosubstituted aromatic)	Complicated pattern in vinyl and aromatic proton region at 7.4–8.0	$2CF_3$'s Major −43.2 (1) Minor −41.3 (1)
$C_6F_5CH=C(SCF_3)(CN)$	1658, 1600, 1524, 1504 (C=C) 3058 (=CH) 2257 (-C≡N) 762 ($-SCF_3$) Strong absorption at 1100 region (-CF)	Single resonance in vinyl region at 7.67 (4, broad), J = 1.2 Hz	$2CF_3$'s Major −42.4 (1) Minor −40.9 (3) J = 3 Hz Three groups of aromatic CF centered at −138.0, −148.6, −161.0
$n\text{-}C_3H_7CH=C(SCF_3)(CN)$		Overlapping CH_2's at 2.58 and 1.63 Overlapping CH_3's at 1.0 2 vinyl H's major, 7.18 (3) J = 7.8 Hz minor, 7.28 (3) J = 7.6 Hz	$2CF_3$'s Major −43.8 (1) Minor −42.2 (1)
$C_6H_5C(CH_3)=C(SCF_3)(CN)$	1592, 1570, 1497 (C=C) 2967, 2874 (-CH) 3086 (=CH) 706 (monosubstituted aromatic) 2227 (-C≡N) 1374 ($-CCH_3$) 1101, 765 ($-SCF_3$)	Aromatic protons at 7.0–7.6 Two CH_3's at *ca.* 2.58 separated by 2 Hz Both unsplit, but smaller one is broad	$2CF_3$'s Major −42.5 (4) J = 0.5 Hz Minor −42.4 (1)
$(C_2H_5)_2C=C(SCF_3)(CN)$	1590 (C=C) 3003, 2976, 2907 (-CH) 2232 (-C≡N) 1110, 762 ($-SCF_3$)	At 220 Mcps two triplets (CH_3's) at 1.12 and 1.22 (J = 7.5 Hz) Two superimposed quadruplets (CH_2's) at 2.65 J = 7.5 Hz	CF_3 −43.1 (1)
	1616 (C=C) 2994, 2907 (-CH) 2227 (-C≡N) 1107, 762 ($-SCF_3$)	Two multisplit CH_2 resonances at 1.90 and 2.78	CF_3 −42.9 (1)

tures, it is concluded that the more prevalent isomer obtained in this reaction is methyl-*cis*-β-(trifluoromethylthio)acrylate (**11a**). Support for this assign-



11a



11b

ment is seen in the infrared spectrum of the trans isomer, which contains a band at 949 cm^{-1}, a frequency consistent with the C–H out-of-plane bending frequency often observed in trans-disubstituted olefins.[11] The predominance of the cis adduct is consistent with several previously studied free-radical additions of thiols to acetylenes.[12]

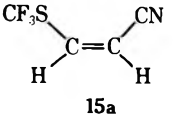
From the ester mixture (**11a** and **11b**) were obtained the acid **12**, acid chloride **13**, amide **14**, and the corresponding nitrile **15** by conventional procedures (eq 15).

$$\underset{\mathbf{11}}{CF_3SCH{=}CHCO_2CH_3} \xrightarrow[H_2O]{HCl} \underset{\mathbf{12}}{CF_3SCH{=}CHCO_2H} \xrightarrow{SOCl_2} \underset{\mathbf{13}}{CF_3SCH{=}CHCOCl} \xrightarrow{NH_3} \underset{\mathbf{14}}{CF_3SCH{=}CHCONH_2} \xrightarrow{P_2O_5} \underset{\mathbf{15}}{CF_3SCH{=}CHCN} \quad (15)$$

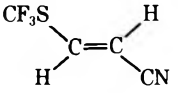
(11) C. N. R. Rao, "Chemical Application of Infrared Spectroscopy," Academic Press, New York, N. Y., 1963, p 152, 153.

(12) The cis adduct arises from a two-step, overall trans addition, and this appears to be the preferred stereochemistry of radical thiol additions to acetylenes: O. Simamura, "The Stereochemistry of Cyclohexyl and Vinylic Radicals," in "Topics in Stereochemistry," Vol. 4, E. L. Eliel and N. L. Allinger, Ed., Wiley, New York, N. Y., 1969, pp 23–25.

The nitrile mixture contained two isomers (ratio 72:28), and the ^1H nmr patterns (Table II) show that, as in the case of the esters, the cis isomer (**15a**) predominates.



15a



15b

Experimental Section

Reaction of Trifluoromethanesulfenyl Chloride with Methyl Acrylate.—Into a quartz tube (12 × 1.5 in.) fitted with a dropping funnel, a gas inlet tube, a magnetic stirrer, and a Dry Ice condenser, was added 92 g (0.673 mol) of liquid CF_3SCl.[13] Freshly distilled methyl acrylate (7 ml) was added, and the mixture was irradiated with a low-pressure mercury resonance lamp for 0.5 hr. This procedure was repeated four times, *i.e.*, until a total of 35 ml (0.388 mol) of methyl acrylate had been added. After the last addition, the mixture was irradiated for 1 hr. The excess CF_3SCl was distilled off, and then the residue was fractionated through a small spinning-band still. There was obtained 40 g (46%) of a 1:1 adduct fraction distilling at 66–72° (25 mm), $n^{25}D$ 1.4152, and 11.83 g (19%) of a 2:1 adduct fraction distilling at 70–72° (0.20 mm), $n^{25}D$ 1.4385. ^{19}F nmr spectra indicated that each fraction contained two major components in ratios of 90:10 (1:1 adduct fraction) and 55:45 (2:1 adduct fraction).

Anal. Calcd for 1:1 adduct $C_5H_6ClF_3O_2S$: C, 27.0; H, 2.7; S, 14.4. Found: C, 27.6; H, 3.1; S, 14.2. Calcd for 2:1 adduct $C_9H_{12}ClF_3O_4S$: C, 35.0; H, 3.9; S, 10.4. Found: C, 35.2; H, 4.2; S, 10.6.

Dehydrochlorination of the 2:1 Methyl Acrylate–CF_3SCl

(13) CF_3SCl (bp 0°) is highly toxic and should be handled only in an efficient hood.

Adduct.—A mixture of 30 g (0.0970 mol) of the 2:1 methyl acrylate–CF_3SCl adduct, 10 g (0.0987 mol) of triethylamine, and 100 ml of tetrahydrofuran was refluxed for a period of 20 hr. A gas chromatogram indicated that a very small amount of starting material remained and that essentially a single product was present. The mixture was filtered and the triethylamine hydrochloride was rinsed and dried on the filter, yield 12.03 g (90%). Distillation of the filtrate through a small Vigreux still yielded 20.78 g (78.4%) of dimethyl α-methylene-α′-(trifluoromethylthio)glutarate distilling at 52° (0.10 mm), $n^{25}D$ 1.4301 (>97% pure by gas chromatography).

Anal. Calcd for $C_9H_{11}F_3O_4S$: C, 39.7; H, 4.1; F, 20.9. Found: C, 39.9; H, 4.1; F, 21.6, 21.3.

The infrared spectrum contains bands at 2994, 2959, and 2849 (saturated CH), 1742 and 1721 (>C=O), 1656 (-C=C-), *ca.* 1110 (broad) (CF), 756 (-SCF_3), and 954 cm^{-1} (CH_2=C<). The ^1H and ^{19}F nmr spectra are tabulated in Table II.

Reaction of Methyl α-(Trifluoromethylthio)-β-chloropropionate with Triethylamine. Preparation of Methyl α-(Trifluoromethylthio)acrylate.—To a solution of 10 g (0.045 mol) of the 1:1 methyl acrylate–CF_3SCl adduct fraction in 75 ml of anhydrous ether was added 6.2 ml of triethylamine. After the resulting mixture was stirred for 0.5 hr, it was filtered and the solid was rinsed on the filter with anhydrous ether. Distillation of the ether solution through a small Vigreux still yielded 6.0 g. (72%) of methyl α-(trifluoromethylthio)acrylate as a colorless liquid distilling at 58–60° (42 mm), $n^{25}D$ 1.4067.

Anal. Calcd for $C_5H_5F_3O_2S$: C, 32.3; H, 2.7; F, 30.6. Found: C, 32.7; H, 2.8; F, 30.3.

Hydrolysis of Methyl α-(Trifluoromethylthio)-β-chloropropionate.—A mixture of 45 g (0.202 mol) of the 1:1 methyl acrylate–CF_3SCl adduct, 60 ml of concentrated HCl, and 300 ml of distilled water was refluxed for 15 hr. The mixture was cooled in an ice–water bath, and the organic layer was separated. Following three extractions of the aqueous layer with 100 ml of ether, the extracts and the organic layer were combined, dried over anhydrous magnesium sulfate, and distilled through a small spinning-band still. After a fraction containing some methyl α-(trifluoromethylthio)acrylate was obtained, 11.04 g (32%) of colorless α-(trifluoromethylthio)acrylic acid distilled at 68–72° (2.00 mm), $n^{25}D$ 1.4213–1.4240.

Anal. Calcd for $C_4H_3F_3O_2S$: F, 33.1; S, 18.6. Found: F, 33.2; S, 17.7.

In addition there was obtained 7.62 g (20%) of a viscous fraction distilling at 97.5–99° (0.025 mm) which contained isomers of (trifluoromethylthio)hydroxypropionic acid. A ^{19}F nmr indicated the presence of two CF_3S-containing materials in a ratio of 85:15.

Anal. Calcd for $C_4H_5F_3O_3S$: C, 25.2; H, 2.6; F, 30.0. Found: C, 25.8, 25.9; H, 2.7, 2.6; F, 30.7, 30.7.

Hydrolysis of Methyl α-(Trifluoromethylthio)acrylate.—A mixture of 11.86 g (0.0636 mol) of methyl α-(trifluoromethylthio)acrylate, 100 ml of distilled water, and 23 ml of concentrated HCl was refluxed for a period of 15 hr. The mixture was cooled, the organic layer was separated, and the aqueous layer was extracted twice with 50 ml of ether. The combined extracts and organic layer were dried over anhydrous magnesium sulfate and distilled through a small Vigreux still. There was obtained 3.62 g (33%) of α-(trifluoromethylthio)acrylic acid as a colorless liquid distilling at 64–69° (1.0 mm), $n^{25}D$ 1.4207, and 3.90 g (32%) of (trifluoromethylthio)-hydroxypropionic acid(s) as a viscous, colorless liquid distilling at 102° (0.7 mm), $n^{25}D$ 1.4284.

Reaction of α-(Trifluoromethylthio)acrylic Acid with Morpholine.—To a stirred solution of 2.0 g (0.01163 mol) of α-(trifluoromethylthio)acrylic acid in 20 ml of anhydrous ether was slowly added 2.20 g (0.0252 mol) of morpholine in 10 ml of ether. After the mixture had stood for 1 hr, it was filtered to remove the product presumed to be morpholinium β-*N*-morpholino-α-(trifluoromethylthio)propionate, yield 3.07 (76%), mp 95°.

Anal. Calcd for $C_{12}H_{21}F_3N_2O_4S$: C, 41.6; H, 6.1; F, 16.4; S, 9.3. Found: C, 41.5; H, 5.8; F, 16.7; S, 9.4.

Conversion of α-(Trifluoromethylthio)acrylic Acid to α-(Trifluoromethylthio)acrylonitrile.—A mixture of 9.0 g (0.0756 mol) of thionyl chloride and 11.09 g (0.0644 mol) of α-(trifluoromethylthio)acrylic acid was stirred at room temperature for 1.5 hr and then at gentle reflux for 6.5 hr. Distillation through a small spinning-band still gave 4.48 g (36%) of α-(trifluoromethylthio)acrylyl chloride distilling at 50–52° (40 mm).

Anhydrous ammonia was passed through 3.56 g (0.019 mol) of this acid chloride in 30 ml of anhydrous ether until there was no further precipitation. The mixture was filtered, the residue was rinsed with ether, and the filtrate and rinsings were combined and evaporated to dryness. The resulting gummy residue was mixed with several grams of anhydrous phosphorus pentoxide and placed in a flask heated by an oil bath and connected through two acetone–Dry Ice cooled traps to the water pump. The system was evacuated, and the oil bath was heated to 160° during 3.5 hr and maintained at 150–160° for 5 hr. There collected in the receiver 0.25 g of colorless liquid, $n^{25}D$ 1.3990. The infrared spectrum contained bands at 3125 and 3021 (=CH), 2232 (conjugated C≡N), 1600 (conjugated C=C), and 758 cm^{-1} (CF_3S).

Preparation of α-(Trifluoromethylthio)acrylonitrile from CF_3SCl and Acrylamide.—Trifluoromethanesulfenyl chloride was passed into a stirred solution of 100 g (1.41 mol) of acrylamide in 500 ml of acetonitrile until 272 g (1.99 mol) of CF_3SCl had been absorbed. The resulting mixture was allowed to stir for a short time, and then the excess reactants were removed *in vacuo* on the oil pump. The liquid residue (267 g) was mixed as well as possible with 430 g of phosphorus pentoxide in a 2-l. flask fitted with an oil bath and a short-path stillhead whose receiver was connected to a water aspirator through two Dry Ice–acetone cooled traps. The flask was also fitted with a paddle stirrer which was manipulated by hand to periodically mix the components as well as possible. The system was evacuated and the oil bath was warmed slowly to 150°. Material began to distill at *ca.* 100°. The oil bath was maintained at 150–180° for 3 hr, whereupon the system was evacuated with an oil pump for an additional few minutes. Distillation of the combined distillate and trap contents through a small spinning-band still gave 10.97 g of a fraction boiling at 44–73° (43 mm), $n^{24}D$ 1.3999. Careful redistillation of this fraction yielded pure α-(trifluoromethylthio)acrylonitrile distilling at 44° (37 mm), $n^{25}D$ 1.3977.

Anal. Calcd for $C_4H_2F_3NS$: F, 37.2; N, 9.1; S, 20.9. Found: F, 37.3; N, 9.3; S, 21.1.

Preparation of (Trifluoromethylthio)acetonitrile. A. Preparation of (Trifluoromethylthio)acetyl Chloride.—Into a solution of 35 g (0.256 mol) of CF_3SCl in 200 ml of anhydrous ether contained in a flask fitted with a magnetic stirrer, an acetone–Dry Ice filled reflux condenser, and a gas addition tube, was passed ketene until the characteristic yellow color of the sulfenyl chloride was gone. After the mixture had stood for 18 hr, it was distilled through a small spinning-band still. There was thus obtained 31.20 g (68%) of (trifluoromethylthio)acetyl chloride distilling at 56° (90 mm), $n^{25}D$ 1.4040–1.4083.

Anal. Calcd for $C_3H_2ClF_3OS$: F, 31.9; S, 18.0. Found: F, 30.7; S, 17.5.

B. Preparation of (Trifluoromethylthio)acetamide.—Ammonia was passed through a stirred and cooled solution of 25 g (0.140 mol) of (trifluoromethylthio)acetyl chloride in 200 ml of anhydrous ether until there was no further reaction. The mixture was warmed to room temperature and then filtered. Upon evaporation of the filtrate *in vacuo*, there was obtained a liquid residue which crystallized when pentane was added, yield 21.05 g (94%), mp 84.5–86.5°. After one recrystallization from benzene, (trifluoromethylthio)acetamide was obtained as colorless plates melting at 88–89°.

Anal. Calcd for $C_3H_4F_3NOS$: C, 22.6; H, 2.5; S, 20.1. Found: C, 22.8; H, 2.6; S, 20.3.

C. Dehydration of (Trifluoromethylthio)acetamide.—A mixture of 10 g (0.0628 mol) of (trifluoromethylthio)acetamide and 10 g (0.0705 mol) of anhydrous P_2O_5 was shaken in a flask until thoroughly mixed. The flask was then fitted with a small still whose receiver was connected through an acetone–Dry Ice cooled trap to a water aspirator. The system was evacuated and then the flask was heated with an oil bath at 160° for at least 0.5 hour. Upon distillation of the combined receiver and trap contents through a small spinning-band still, there was obtained 5.8 g (65%) of (trifluoromethylthio)acetonitrile as a colorless liquid distilling at 59° (34 mm), $n^{25}D$ 1.3831.

Anal. Calcd for $C_3H_2F_3NS$: C, 25.7; H, 1.4; N, 9.9; S, 22.7. Found: C, 26.2; H, 1.6; N, 10.2; S, 23.6.

Reaction of Carbonyl Compounds with (Trifluoromethylthio)-acetonitrile.—All of these reactions were carried out in about the same manner. The reaction with benzaldehyde is described below in detail. The results of the other experiments are given in Tables III, IV, and V.

A mixture of 16 g (0.151 mol) of benzaldehyde, 20 g (0.142 mol) of (trifluoromethylthio)acetonitrile, 3 ml of piperidine, and 145 ml of benzene was refluxed in an apparatus fitted with a water separator. After 0.5 hr of refluxing, the separation of water had stopped. The reaction mixture was extracted twice with 50 ml of water, twice with 50 ml of 3% aqueous hydrochloric acid, and once with 50 ml of saturated aqueous sodium bicarbonate solution. After being dried over anhydrous magnesium sulfate, the mixture was distilled. There was thus obtained 23.06 g (83%) of β-phenyl-α-(trifluoromethylthio)acrylonitrile as a colorless liquid distilling at 69° (0.15 mm), $n^{25}D$ 1.5509.

Anal. Calcd for $C_{10}H_6F_3NS$: F, 24.9; S, 14.0. Found: F, 25.1; S, 13.6.

A ^{19}F nmr spectrum on a similar mixture after the distillation of the benzene, but before the distillation of the product, showed two major fluorine-containing components which are presumably the cis and trans isomers in a ratio of 90.1:8.6. Distillation through a spinning-band still gave a fraction which was 98% one isomer.

Addition of Trifluoromethanethiol to Methyl Propiolate.—A mixture of 42 g (0.50 mol) of methyl propiolate and 62 g (0.607 mol) of trifluoromethanethiol contained in a quartz tube (12 × 1.5 in.) fitted with a Dry Ice condenser was irradiated with a spiral-shaped, low-pressure mercury resonance lamp for 46.25 hr. After the excess volatiles had been allowed to evaporate, the reaction mixture was distilled through a small spinning-band still. There was obtained 14.09 g of recovered methyl propiolate and 35.25 g (57%) of a 1:1 adduct fraction distilling at 62° (95 mm) and 46° (13 mm). There remained 20.12 g of viscous residue.

Anal. Calcd for $C_5H_5F_3O_2S$: C, 32.3; H, 2.7; F, 30.6. Found: C, 32.8; H, 3.0; F, 31.6.

A gas chromatogram indicated the presence of both the cis and trans isomers in a ratio of 77.5 (cis):22.5 (trans). Pure samples of each were obtained by preparative-scale gas chromatography with a 12 ft × 0.75 in. column packed with 20% "Diglyceride" on Chromasorb at 125°.

Methyl *cis*-β-(trifluoromethylthio)acrylate had bp 56° (20 mm), $n^{24}D$ 1.4246.

Anal. Calcd for $C_5H_5F_3O_2S$: C, 32.3; H, 2.7; F, 30.6; S, 17.2. Found: C, 32.7; H, 2.5; F, 30.6; S, 17.3.

Methyl *trans* β-(trifluoromethylthio)acrylate (not distilled) had $n^{24}n$ 1.4211.

The ^1H and ^{19}F nmr spectra of these isomers are tabulated in Table II.

Hydrolysis of Methyl β-(Trifluoromethylthio)acrylate (Cis and Trans Isomers).—A mixture of 62 g (0.335 mol) of methyl β-(trifluoromethylthio)acrylate, 1 l. of distilled water, and 250 ml of concentrated HCl was refluxed for 18.5 hr. After being cooled to room temperature, the mixture was extracted three times with 200 ml of ether. The extracts were dried over anhydrous magnesium sulfate and distilled through a small Vigreux still. There was obtained 5.80 g of recovered methyl β-(trifluoromethylthio)acrylate and 45.15 g (87%) of β-(trifluoromethylthio)acrylic acid as a colorless liquid distilling at 93–96° (13 mm).

Anal. Calcd for $C_4H_3F_3O_2S$: C, 27.9; H, 1.8; F, 33.1. Found: C, 28.1; H, 1.7; F, 32.3.

Conversion of β-(Trifluoromethylthio)acrylic Acid to β-(Trifluoromethylthio)acrylonitrile. A. Preparation of β-(Trifluoromethylthio)acrylyl Chloride.—A mixture of 100.7 g (0.583 mol) of β-(trifluoromethylthio)acrylic acid and 60 ml of thionyl chloride was stirred for 16 hr and then gently refluxed for 4 hr. Upon distillation of the reaction mixture through a small spinning-band still there was obtained 73 g (65.5%) of β-(trifluoromethylthio)acrylyl chloride distilling at 48° (29 mm), $n^{25}D$ 1.4553. There was also recovered 16.5% of β-(trifluoromethylthio)acrylic acid.

B. Preparation of β-(Trifluoromethylthio)acrylamide.—Ammonia was passed through an ice-cooled solution of 11.6 g (0.0746 mol) of β-(trifluoromethylthio)acrylyl chloride in 100 ml of anhydrous ether until there was no more precipitation. The reaction mixture was filtered, the solid was rinsed on the filter with ether, and the filtrate and rinsings were evaporated to dryness. There was obtained 9.88 g (94%) of crude β-(trifluoromethylthio)acrylamide melting at 95–98°. After recrystallization from benzene (11 ml/g), the product was obtained as fine white needles melting at 102–102.5°.

Anal. Calcd for $C_4H_4F_3NOS$: F, 33.3; N, 8.2; S, 18.7. Found: F, 34.1; N, 8.0; S, 17.6.

C. Dehydration of β-(Trifluoromethylthio)acrylamide.—A mixture of 8.85 g (0.0577 mol) of finely ground β-(trifluoromethylthio)acrylamide and 25 g (0.176 mol) of anhydrous P_2O_5 was placed in a small, round-bottomed flask fitted with an oil bath and a small still head whose receiver was connected through an acetone–Dry Ice cooled trap to a water aspirator. The system was evacuated, and during 2.5 hr the oil bath was heated to 175°. During this time, 6.76 g of distillate collected in the receiver. Distillation of this material through a small spinning-band still yielded 5.29 g (67%) of β-(trifluoromethylthio)acrylonitrile distilling at 62° (48 mm), $n^{25}D$ 1.4203.

Anal. Calcd for $C_4H_2F_3NS$; F, 37.2; N, 9.1; S, 20.9. Found: F, 36.8; N, 9.4; S, 21.4.

The infrared spectrum is consistent with a mixture of the cis and trans isomers of β-(trifluoromethylthio)acrylonitrile: ir 3067 (=CH), 2217 (-C≡N), 1577 (C=C), 1111 (CF), 756 (-SCF_3), 950 (trans CH=CH), 711 cm^{-1} (cis CH=CH). A gas chromatogram showed the presence of two isomers in a ratio of 70.5 (cis):29.5 (trans). Samples of each were separated with a 12 ft × 0.75 in. column packed with 20% "Diglyceride" on Chromosorb at 100°.

***cis*-β-(Trifluoromethylthio)acrylonitrile** had bp 62° (45 mm), $n^{24}D$ 1.4158.

Anal. Calcd for $C_4H_2F_3NS$: F, 37.2; N, 9.1; S, 20.9. Found: F, 37.2; N, 9.3; S, 20.6.

***trans*-β-(Trifluoromethylthio)acrylonitrile** had bp 64° (45 mm), $n^{24}D$ 1.4242.

The ^1H and ^{19}F nmr resonances of these isomers are tabulated in Table II.

Nmr and Infared Spectra.—^{19}F nmr spectra (56.4 MHz) were obtained from 10% solutions of the compounds in carbon tetrachloride with a Varian A-56/60 spectrometer. All ^1H nmr spectra were also obtained from carbon tetrachloride solutions with a Varian A-60 spectrometer, except in one case (Table V) in which a Varian HR-220 spectrometer was used. The ^{13}C spectrum (25.1 MHz) was obtained with a Varian HA-100 spectrometer modified for noise decoupling. Chemical shifts are reported in parts per million from the resonance of tetramethylsilane (^1H) or fluorotrichloromethane (^{19}F) as internal standards and methyl iodide (^{13}C) as an external standard. In accordance with the recommendations published in ASTM E-386-69 T, chemical shifts at higher field than the resonance of the standard are designated as negative.

The infrared spectra were determined with a Perkin-Elmer 21 (prism) spectrometer.

Registry No.—**1**, 34033-72-2; **3**, 34033-73-3; **4**, 34033-74-4; **5**, 13122-60-6; **6**, 13137-45-6; **7**, 34033-77-7; **8**, 34145-34-1; **9**, 7347-10-6; **10**, 34033-79-9; **11**, 13122-56-0; **11a**, 34033-81-3; **11b**, 34033-82-4; **12**, 7347-02-6; **13**, 7347-01-5; **14**, 7347-00-4; **15a**, 34033-86-8; **15b**, 34033-87-9; (trifluoromethylthio)-acetyl chloride, 1645-79-0; (trifluoromethylthio)acetamide, 1737-79-7.

Bis(trifluoromethyl)thioketene. II. Acyclic Derivatives

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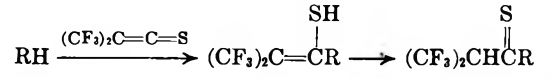
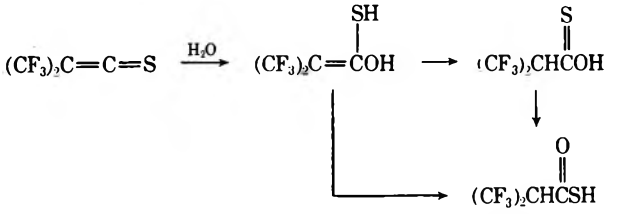
Bis(trifluoromethyl)thioketene adds to alcohols and thiols to form thio esters and to amines to give thioamides. With 1,3-disubstituted triazenes compounds of the formula $ArSC(=NR)CH(CF_3)_2$ are formed. Dimethylanilines give $ArN(CH_3)CH_2SCH=C(CF_3)_2$ and ethers form $ROCHRSCH=C(CF_3)_2$. Silicon and tin hydrides add to yield products with sulfur–metal bonds. Olefinic compounds undergo ene reactions to produce compounds containing the $C=CC-SCH=C(CF_3)_2$ unit. More complex transformations take place with cycloheptatriene, bicyclobutane, and bicyclo[4.2.0]oct-7-ene. C-Thioacylations occur with indole, 1,3,3-trimethyl-2-methyleneindoline, and 6-(dimethylamino)fulvene. Reaction with sulfur diimides yields ketenimines of the formula $(CF_3)_2C=C=NR$.

Synthesis and cycloaddition reactions of bis(trifluoromethyl)thioketene were reported in part I.[1] This paper describes acyclic derivatives to illustrate further the range of reactivity of the thioketene.

Addition to Water, Alcohol, and Thiols.—The reactivity of bis(trifluoromethyl)thioketene resides, in most instances, in the thiocarbonyl group, as reflected in its cycloaddition reactions. Normal additions to active hydrogen compounds are therefore believed to proceed through the enethiol.



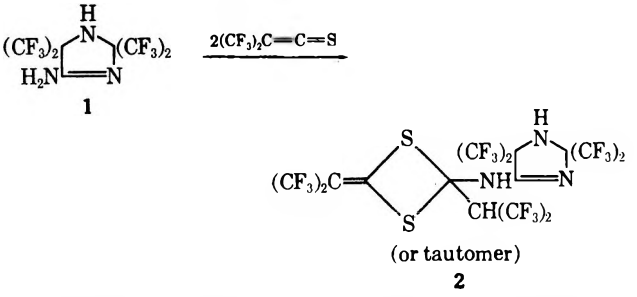
In the special case of water, a thiono acid may be another possible intermediate.



Addition of methanol or ethanol forms $(CF_3)_2CHC(=S)OR$ which, like certain other sulfur compounds,[2] produces white, faintly oxyluminescent fumes in air, a phenomenon that has been attributed to the formation of sulfur monoxide. Thio adducts do not give obvious fumes. Addition of benzeneselenol results in the novel function, $-C(=S)Se-$. Thio esters derived from the thioketene are listed in Table I.

Addition to Hydrogen Bromide.—The thioketene and HBr form $(CF_3)_2CHC(=S)Br$. Few thioacyl bromides are known. Besides thiocarbonyl bromide,[3] a complex thioacyl bromide[4] has been reported.

Thioacylation of Amines.—Catalytic amounts of tertiary amines, except for *N*,*N*-dimethylanilines, cause the thioketene to dimerize, but with primary and secondary amines addition takes place much more rapidly than dimerization and high yields of thioamides are obtained (Table I). Ordinarily, a second molecule of the thioketene does not add to the thiocarbonyl group of the thioamides to form a 1,3-dithietane. However, in the case of the aminoimidazoline[5] **1**, only the diadduct **2** can be obtained, even when excess imidazoline is used.

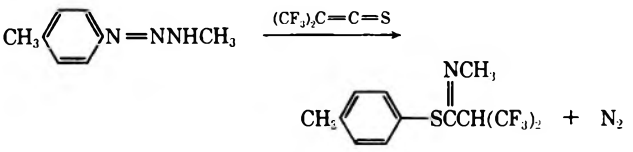


1

(or tautomer)

2

Bis(trifluoromethyl)thioketene and 1-methyl-3-*p*-tolyltriazene result in the unusual reaction shown below, which is also operable with 1,3-di-*p*-tolyltriazene.



Thioacylation of the triazene seems likely as the first step in the reaction sequence and product formation might be rationalized as shown in Scheme I.

Besides physical evidence, proof of structure of the product includes hydrolysis to *p*-toluenethiol. 3,3-Dimethyl-1-*p*-tolyltriazene dimerized the thioketene.

(1) M. S. Raasch, *J. Org. Chem.*, **35**, 3470 (1970). To the literature synopsis therein may be added: (a) Reaction of alkylthiophenylacetylenes with amines to form phenylthioacetamides is postulated to proceed through phenylthioketene. M. L. Petrov, B. S. Kupin, and A. A. Petrov, *Zh. Org. Khim.*, **5**, 1759 (1969); *J. Org. Chem. USSR*, **5**, 1705 (1969). (b) Pyrolysis of 1,1-diphenyl-2-ethoxy-2-(ethoxythiocarbonylthio)ethylene or ethyl diphenylthionoacetate gave diphenylthioketene dimer. A. Schönberg, W. Knöfel, E. Frese, and K. Praefcke, *Chem. Ber.*, **103**, 949 (1970). (c) Carbomethoxycyanothioketene, generated *in situ*, combines with 2-methylthiobenzhydrazide to form mesoionic 2-(carbomethoxycyanomethylene)-4-methyl-5-phenyl-1,3,4-thiadiazole. R. Grashey, M. Baumann, and R. Hamprecht, *Tetrahedron Lett.*, 5083 (1970). (d) Perfluoroisobutene reacts with sulfur and potassium fluoride to form $(CF_3)_2C=C=S$ dimer. B. L. Dyatkin, S. R. Sterlin, L. G. Zhuravkova, and I. L. Knunyants, *Dokl. Akad. Nauk SSSR*, **183**, 598 (1968); *Proc. Acad. Sci. USSR*, **183**, 1018 (1968). (e) Reaction of perfluoroisobutene with potassium diethyl thiophosphate, potassium thiocyanate, or sodium thiosulfate forms $(CF_3)_2C=C=S$ dimer. I. L. Knunyants, B. L. Dyatkin, S. R. Sterlin, and V. L. Isaev, Russian Patent 246,508 (1969). (f) Perfluoroisobutene and potassium sulfide yield $(CF_3)_2C=C=S$ dimer. D. C. England, U. S. Patent 3,544,591 (1970); *Chem. Abstr.*, **74**, 141735h (1971). (g) Bis(trifluoromethyl)thioketene adds to carbodiimides and azines to give 1,3-thiazetidines. M. S. Raasch, U. S. Patent 3,592,811 (1971); *Chem. Abstr.*, **75**, 99232k (1971). (h) Reaction of lithium 2-phenylethynethiolate with protic substances presumably proceeds through phenylthioketene. R. Raap, *Can. J. Chem.*, **46**, 2251 (1968). (i) Thioketene ions appear in the mass spectra of desaurins. P. Yates, T. R. Lynch, and L. S. Weiler, *ibid.*, **46**, 365 (1968). (j) The potential role of thioketene intermediates in the dimerization of *N*-alkyl-3-isothiazolones to 2,4-dimethylene-1,3-diethietanes is discussed. A. W. K. Chan, W. D. Crow, and I. Gosney, *Tetrahedron*, **26**, 1493 (1970).

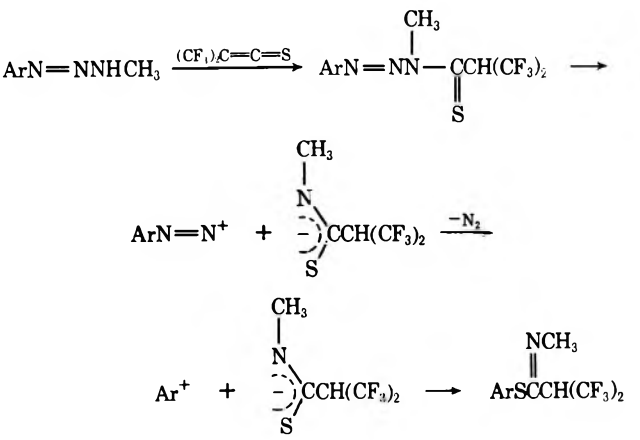
(2) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. IV, Chemical Publishing Co., New York, N. Y., 1962, pp 179, 180.

(3) W. J. Middleton, E. G. Howard, Jr., and W. H. Sharkey, *J. Org. Chem.*, **30**, 1375 (1965); R. Steudel, *Angew. Chem.*, **79**, 649 (1967); *Angew. Chem., Int. Ed. Engl.*, **6**, 635 (1967).

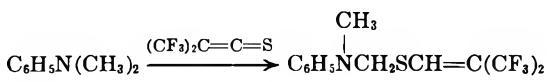
(4) B. R. O'Connor and F. N. Jones, *J. Org. Chem.*, **35**, 2002 (1970).

(5) W. J. Middleton and C. G. Krespan, *ibid.*, **35**, 1480 (1970).

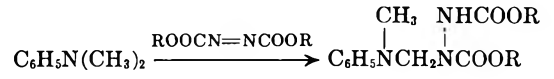
SCHEME I



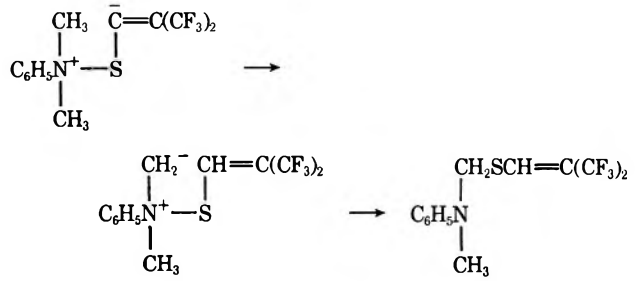
Reaction with *N,N*-Dimethylanilines.—The thioketene adds to *N,N*-dimethylanilines at 10° with attack on one methyl group. The reaction is reminiscent of



the addition of azodicarboxylic ester to dimethylaniline, the mechanism of which has been concluded to be ionic.[6]



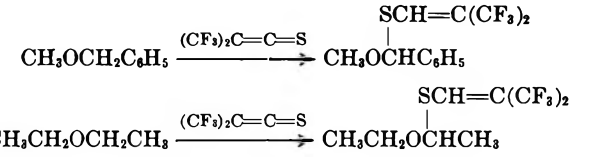
Like the azodicarboxylic ester reaction, the thioketene reaction proceeds more slowly with *N,N*-dimethyl-*m*-nitroaniline than with *N,N*-dimethylaniline, does not go with *N,N*-dimethyl-*p*-nitroaniline under the conditions, and is not stopped by diphenylpicrylhydrazyl. Adapting the rationalization used for the azodicarboxylic ester reaction to the present case, electrophilic attack on the nitrogen atom first takes place, then proton transfer and ylide rearrangement.



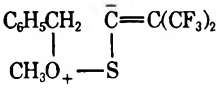
The reaction also proceeds well with *N,N*-dimethyl-*p*-toluidine, and with *N,N,N',N'*-tetramethylbenzidine to give a diadduct. However, with *N*-ethyl-*N*-methylaniline or *N,N*-dimethyl-1-naphthylamine the reaction is apparently slowed to the point where the sensitive, base-catalyzed dimerization of the thioketene takes precedence.

The $(CF_3)_2C{=}CHS-$ group, encountered in the above compounds and many that follow, has in its ^1H nmr spectrum a diagnostic quadruplet, J = 1.4–1.6 Hz, at about 7.5 ppm, a position seldom occupied by other absorptions.

Addition to Ethers.—Reaction of the thioketene with ethers is another example of the introduction of a propenylthio group.

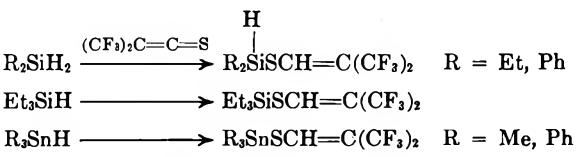


This reaction, like the addition to dimethylaniline, could be represented as proceeding through a dipolar intermediate.

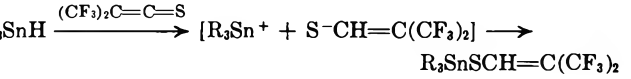


However, the reaction is peroxide catalyzed and is considered to be a free radical reaction. Peroxide catalysis also leads to more complex products.

Adducts with Silicon and Tin Hydrides.—These hydrides also add to the thioketene to form the $(CF_3)_2C{=}CHS-$ group with its characteristic nmr.

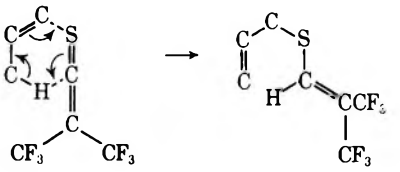


The product from trimethylstannane is unstable. The reaction can be compared with the addition of triethylstannane to phenyl isothiocyanate, which adds in the same direction.[7] Presumably it is ionic with nucleophilic attack of hydride hydrogen on carbon, *e.g.*,



Ene Reactions.—A range of olefinic substances readily undergoes the ene reaction[8] with the thioketene as illustrated in Table II. The olefin attaches to the sulfur atom and in this respect the thioketene resembles hexafluorothioacetone[9a] and aryl thioketones in their reaction with tetramethylallene.[9b]

The ene reaction is usually, though not necessarily, represented as a concerted reaction proceeding through a six-membered transition state.



In the reaction of the thioketene with allene, two linear molecules, to form $(CF_3)_2C{=}CHSCH_2C{\equiv}CH$ some modification of the picture is needed.[10]

If a diradical were an intermediate, cyclization to form a thietane would be a possibility in addition to the ene product. No careful search for the thietanes

(6) R. Huisgen and F. Jacob, *Justus Liebigs Ann. Chem.*, **590**, 46 (1954).

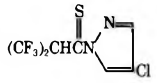
(7) J. G. Noltes and M. J. Janssen, *J. Organometal. Chem.*, **1**, 346 (1964).

(8) For a review of the ene reaction see H. M. R. Hoffmann, *Angew. Chem.*, **81**, 597 (1969); *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969).

(9) (a) W. J. Middleton, *J. Org. Chem.*, **30**, 1395 (1965); (b) H. Gotthardt, *Tetrahedron Lett.*, 2343, 2345 (1971).

(10) W. R. Dolbier, Jr., and Sheng-Hong Dai, *Chem. Commun.*, 166 (1971), propose that allene and hexafluorocyclobutanone undergo a concerted reaction passing through a distorted, cyclic, six-membered, dipolar transition state. W. H. Urry, J. H. Y. Niu, and L. G. Lundsted, *J. Org. Chem.*, **33**, 2302 (1968), suggest a zwitterion intermediate in the reaction of allene with hexafluoroacetone. R. L. Adelman, *ibid.*, **33**, 1400 (1968), argues for a four-membered, cyclic, dipolar intermediate for the ene reaction of olefins with hexafluoroacetone.

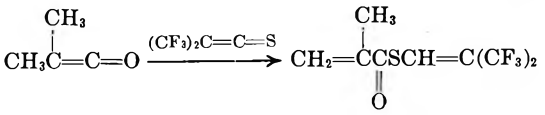
TABLE I
ESTERS AND AMIDES FROM BIS(TRIFLUOROMETHYL)THIOKETENE[d]

Reactant	Reaction conditions	Product	Registry no.	Yield, %	Bp (mm) or mp, °C	$n^{24}D$	Color
CH_3OH	CH_2Cl_2	$(CF_3)_2CHC(=S)OCH_3$	33830-41-0	69	94–96	1.3588	Pale yellow
C_2H_5OH	CH_2Cl_2	$(CF_3)_2CHC(=S)OC_2H_5$	867-93-6	84	110–111	1.3622	Pale yellow
C_2H_5SH	CH_2Cl_2	$(CF_3)_2CHC(=S)SC_2H_5$	33830-42-1	88	62.6 (23)	1.4382	Orange
$(CH_3)_2CHSH$	CH_2Cl_2	$(CF_3)_2CHC(=S)SCH(CH_3)_2$	33830-43-2	85	62–64 (23)	1.4322	Orange
$C_6H_5CH_2SH$	CH_2Cl_2	$(CF_3)_2CHC(=S)SCH_2C_6H_5$	33830-44-3	92	65 (0.3)	1.5136	Orange
C_6H_5SH		$(CF_3)_2CHC(=S)SC_6H_5$	33830-45-4	82	100 (10) Mp 37.5–38.5	1.5044	Orange
p-ClC_6H_4SH[a]	100°, 5 hr	$(CF_3)_2CHC(=S)SC_6H_4Cl$-*p*	33830-46-5	81	74–75 (0.5) Mp 34		Red-orange
C_6H_5SeH[a]		$(CF_3)_2CHC(=S)SeC_6H_5$	33830-47-6	96	112–114 (13)	1.525	Magenta
$CH_2=CHCH_2NH_2$	CH_2Cl_2	$(CF_3)_2CHC(=S)NHCH_2CH=CH_2$	33830-48-7	64	67–68 (16)	1.4345	Orange
$C_6H_5CH_2NH_2$	CH_2Cl_2	$(CF_3)_2CHC(=S)NHCH_2C_6H_5$	33830-49-8	49	Mp 64–66 (hexane)		Pale yellow
p-$ClC_6H_4NH_2$	C_6H_6	$(CF_3)_2CHC(=S)NHC_6H_4Cl$-*p*	7527-43-7	84	Mp 54.5–55.5 (petroleum ether)		Yellow
$C_6H_5NHCH_3$	Hexane	$(CF_3)_2CHC(=S)N(CH_3)C_6H_5$	33820-51-2	83	Mp 77.5–78.5 (hexane)		Pale yellow
p-$CH_3C_6H_4NHCH_3$[a]	CH_2Cl_2	$(CF_3)_2CHC(=S)N(CH_3)C_6H_4CH_3$-*p*	33830-52-3	71	Mp 70–70.7 (CH_3OH)		Yellow
$C_6H_5CH=NNHCH_3$[b]	CH_2Cl_2	$(CF_3)_2CHC(=S)N(CH_3)N=CHC_6H_5$	33830-53-4	85	Mp 143–144 (CH_3OH)		Yellow
	CH_2Cl_2		33830-54-5	81	37 (0.1)	1.4872	Red-orange

[a] Eastman Kodak Co., Rochester, N. Y. [b] R. H. Wiley and G. Irick, *J. Org. Chem.*, **24**, 1925 (1959). [c] R. Hüttel, O. Schäfer, and G. Welzel, *Justus Liebigs Ann. Chem.*, **598**, 186 (1956). [d] Satisfactory analytical data (±0.33% for C, H, and S) were reported for all new compounds listed in the table except that no. 8 was analyzed for F instead of S.

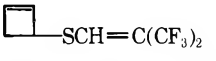
was made aside from observing the nmr spectra. The ^{19}F shift for the thietanes[1] is farther downfield than for ene products. Only in the case of α-methylstyrene in Table II were both products observed, probably the result of separate reaction paths rather than a common intermediate.

Dimethylketene and butylethylketene react with the thioketene to form acrylate thio esters, whereas



ketene and methylketene cycloadd to form thietanes.[1] The greater electron donation to C=C in $(CH_3)_2C=C=O$ *vs.* $CH_3CH=C=O$ promotes the ene reaction. This effect has been observed in other ene reactions.[8]

1-Methylcyclopropene, cyclopentene, and cyclohexene readily underwent the ene reaction at 15–25° but cyclobutene required a higher temperature. At 100° a mixture was formed. Purification by glpc was hampered by polymerization on the column but a small amount of material identified as $CH_2=CHCH=CHSCH=C(CF_3)_2$ was obtained. This could arise by ring opening of the primary ene product, shown below.



Hexamethyl Dewar benzene gave an ene reaction, apparently the first reported for this compound.

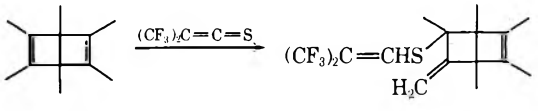
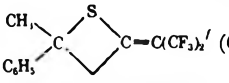
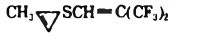
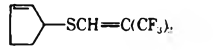
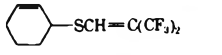
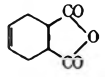
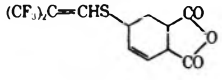
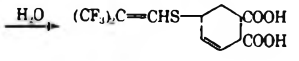
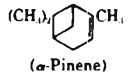
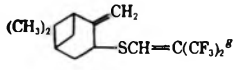
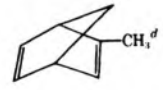
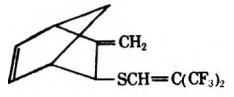
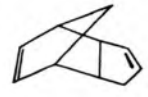
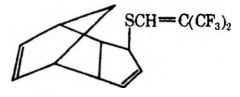
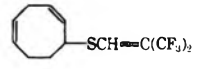
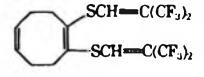
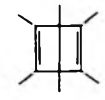
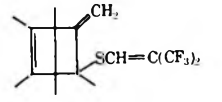


TABLE II

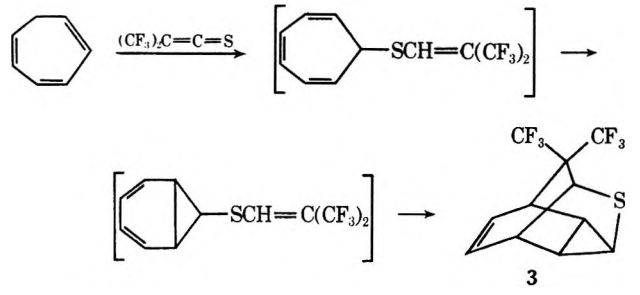
ENE REACTIONS. 3,3,3-TRIFLUORO-2-(TRIFLUOROMETHYL)PROPENYL SULFIDES[a,i]

Reactant	Reacn condn	Product	Registry no.	Bp, °C (mm)	$n^{25}D$	Yield, %
$CH_2=CHCH_3$	100°, 3 hr	$CH_2=CHCH_2SCH=C(CF_3)_2$	28181-98-8	52.5–53 (15)	1.4048	61
$CH_2=C=CH_2$	100°, 15 hr	$CH\equiv CCH_2SCH=C(CF_3)_2$	33830-56-7	62.5–63 (22)	1.4080	>42
$(CH_3)_2C=C(CH_3)_2$	24–30°	$CH_2=CCH_2C(CH_3)_2SCH=C(CF_3)_2$	30589-11-8	58 (7)	1.4200	88
$CH_2=CHCH_2Cl$	100°, 16 hr	$ClCH=CHCH_2SCH=C(CF_3)_2$	33835-26-6	68 (8)	1.4360	27
		65:35 cis:trans	33835-27-7			
$CH_2=C(CH_3)COOCH_3$	24°, 16 hr Reflux, 4 hr	$CH_2SCH=C(CF_3)_2$ $CH_2=C(CH_2SCH=C(CF_3)_2)COOCH_3$	33830-58-9	82 (1)	1.4250	27
$C_6H_5CH_2CH=CH_2$	100°, 2 hr	$C_6H_5CH=CHCH_2SCH=C(CF_3)_2$[e]	33835-28-8	73–77 (0.1)	1.5062	70
p-$CH_3OC_6H_4CH=CHCH_3$ (Anethole)	24°, 16 hr	p-$CH_3OC_6H_4CH(SCH=C(CF_3)_2)CH_2$	33830-59-0	Mp 77 (MeOH)		72
$C_6H_5C(CH_3)=CH_2$	24°, 20 hr	$C_6H_5C(CH_2SCH=C(CF_3)_2)=CH_2$[f] (39%)	28182-02-7		1.4916	
		 [f] (61%)	23592-39-4	60 (0.05)	1.4875	65
$(CH_3)_2C=C=O$[a]	0–34°, 2 hr EtOAc	$CH_2=CCH_2COSCH=C(CF_3)_2$	33872-30-9	80–81 (23)	1.4234	40
$CH_3CH_2C(C_4H_9)=C=O$[b]	24°, 16 hr Hexane	$CH_3CH=C(C_4H_9)COSCH=C(CF_3)_2$	33830-62-5	47–49 (0.1)	1.4417	75
$CH_3C(CH_3)=CHCH=CCH_3$	24°, 2 hr 100°, 1 hr	$CH_2=C(CH_3)CHCH=CCH_3$ $SCH=C(CF_3)_2$	33830-63-6	84–85 (5)	1.4393	60
	0°, CH_2Cl_2		33830-64-7	65–68 (11)	1.4210	31
	24°, 1 hr		30631-75-5	97–99 (32)	1.4345	89
	24°, 1 hr		28181-99-9	112–114 (29)	1.4455	72
	C_6H_6, 100°, 20 hr		33830-67-0	Mp 72–73 (CCl_4)		65
			33830-81-8	Mp 157 ($MeNO_2$)		
 (α-Pinene)	24°, 16 hr	 [g]	30589-17-4	69–70 (0.3)	1.4568–1.4605	85
 [d]	24°, 1 hr		33830-82-9	91 (4.6)	1.4668	83
	24°, 20 hr		28182-01-6	70 (0.1)	1.4773	92
	24°, 3 hr		28182-00-5	49 (0.05)	1.4621	23, 50
			33872-35-4	95 (0.05)	1.4750	34, 15
	24°, 16 hr		33830-85-2	61 (0.4)[h]	1.4514	96

[a] C. W. Smith and D. G. Norton in "Organic Syntheses," Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, pp 348–350. [b] Eastman Chemical Products, Inc., Kingsport, Tenn. [c] F. Fisher and D. E. Applequist, *J. Org. Chem.*, **30**, 2089 (1965); R. M. Magid, T. C. Clarke, and C. D. Duncan, *ibid.*, **36**, 1320 (1971). [d] C. A. Cohen, French Patent 1,478,766 (1967); *Chem. Abstr.*, **68**, 12554a (1968). [e] Similarity of nmr spectrum to that of anethole indicates trans form. [f] Compounds separated by glpc on column containing 20% Triton X305 (Rohm and Haas Co.) on firebrick. [g] Two stereoisomers. [h] Distillation bath at 100°. [i] Disclosed in part in M. S. Raasch, U. S. Patent 3,536,765 (1970); *Chem. Abstr.*, **74**, 4232c (1971). [j] Satisfactory analytical data (±0.4%) for C, H, and S were reported for all new compounds listed in the table.

Natural rubber in solution reacted with the thioketene to form a composition containing 30% by weight of the thioketene.

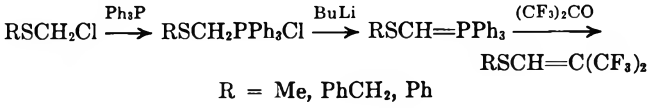
Cycloheptatriene Adduct.—Cycloheptatriene and bis(trifluoromethyl)thioketene, containing a total of five double bonds, react at 25° in a 1:1 ratio to give a compound **3**, revealing only one double bond in its Raman spectrum. This has been rationalized as proceeding through an ene reaction, bond rearrangement to a norcaradiene, and intramolecular Diels–Alder addition of the side chain to the norcaradiene to form the proposed structure **3**.



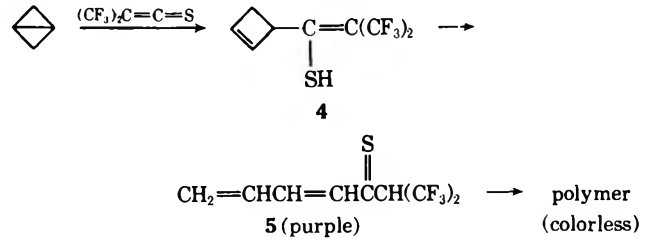
3

The nmr spectra and other physical data are described in the Experimental Section. A model of the structure poses no problems. The first two steps are analogous to those proposed for the addition of dimethyl acetylenedicarboxylate to cycloheptatriene.[11a] A favorable situation for the intramolecular Diels–Alder addition is assumed, as $(CF_3)_2C{=}CHSCH_3$ and $(CF_3)_2C{=}CHSC_6H_5$ do not add to cycloheptatriene or 2,3-dimethylbutadiene at 100°.

The vinyl sulfides were made by the following sequence and served also as nmr and ir reference compounds.



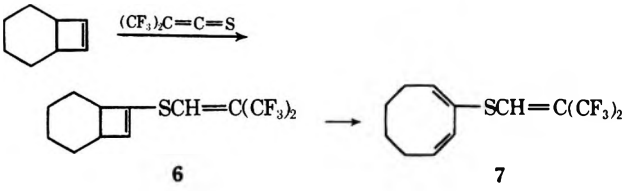
Addition to Bicyclobutane.—Addition of the thioketene to bicyclobutane gave short-lived products in a course different from the conventional ene reaction.



4

When equivalent amounts of the reactants were mixed at 0° in deuteriochloroform and the solution was placed in a cold ir cell, a strong band was observed for SH at 2550 cm^{-1}, at 1588 cm^{-1} for exocyclic C=C, and at 1562 cm^{-1} for cyclobutene C=C. After 10 min the sample had become purple with weaker SH and C=C bands. After 16 min the SH band had disappeared. The nmr spectra were in accord with the structure **4** (see Experimental Section). With development of the purple color, nmr showed the appearance of the $(CF_3)_2CH$ group, disappearance of cyclobutene CH=CH, and appearance of new unsaturation. The purple color is indicative of a conjugated thiocarbonyl group. From these considerations, structure **5** is proposed for the purple compound, formed by ring opening of the cyclobutene. Clean conversion to **5** was frustrated by concomitant polymerization. The end product was a colorless, tacky polymer.

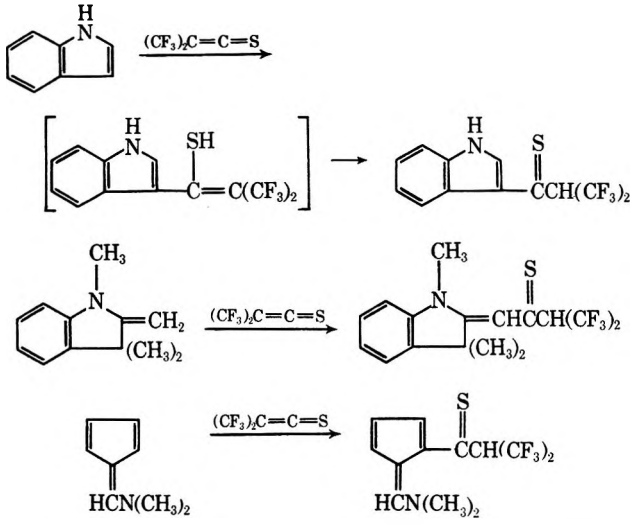
Addition to Bicyclo[4.2.0]oct-7-ene.—The thioketene substitutes on the cyclobutene ring to form a compound **6** that is isomerized by heat with opening of the cyclobutene ring to form a 1,3-cyclooctadiene **7**.



6 **7**

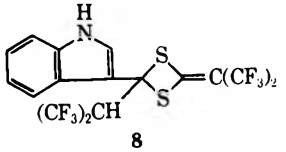
The ^1H nmr of the initial adduct reveals the $(CF_3)_2C{=}CH$ group and one cyclobutene =CH. Incipient isomerization was noted at 50° in an nmr tube. At 95°, isomerization became complete. The final product was identified by nmr and ir spectrum and by oxidation to adipic acid.

C-Thioacylations.—Indole, 1,3,3-trimethyl-2-methyleneindoline, and 6-(dimethylamino)fulvene are thioacylated at 25° by the thioketene.



These colored thioketones can be regarded as vinylogs of thioamides, having one, one, and three vinylene groups, respectively, between the thiocarbonyl group and the nitrogen atom. They are dipole stabilized; *i.e.*, a resonance form can be written in which a negative charge resides on the sulfur atom and a positive charge on the nitrogen.

These thioketones form unstable dithietanes with another mole of the thioketene, *e.g.*,



8

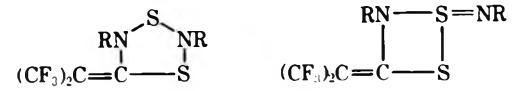
(11) (a) M. J. Goldstein and A. H. Gevirtz, *Tetrahedron Lett.*, 4413 (1965); (b) D. H. Clemens, A. J. Bell, and J. L. O'Brien, *ibid.*, 1487, 1491 (1965).

Ketenimines from Sulfur Diimides.—The thioketene reacts with sulfur diimides to give ketenimines in 20–48% yield.

$$RN{=}S{=}NR \xrightarrow{(CF_3)_2C{=}C{=}S} (CF_3)_2C{=}C{=}N{-}R$$

R = Me, *n*-Bu, *tert*-Bu, Ph

No evidence for mechanism is available, as the by-products were resinous. However, the reaction may proceed through a five- or four-membered ring.



Phenyl isothiocyanate reacts with sulfur diimides analogously.[11b]

Experimental Section

The ^1H nmr spectra were determined on a Varian A-60 instrument using tetramethylsilane as external standard. The ^{19}F nmr spectra were measured on a Varian A-56/60 instrument using 1,2-difluoro-1,1,2,2-tetrachloroethane as a standard in a capillary tube placed in the sample tube. With this standard, nearly all values for the compounds of this article fall within 1000 Hz downfield (−) for the standard. This standard is 3800 Hz (67.4 ppm) upfield from chlorotrifluoromethane. Raman spectra were measured on Cary Model 81 Laser, ir on Perkin-Elmer Model 21 and uv on Cary 14 spectrometers. Melting and boiling points are uncorrected.

Esters and Amides (Table I).—To the reactant in the solvent specified, stirred and cooled in an ice bath, bis(trifluoromethyl)-thioketene was added dropwise at such a rate as to keep the temperature at 15–25°. The reaction with *p*-ClC_6H_4SH at 100° was carried out in a sealed glass tube. In simple esters and amides the nmr septuplet (J = 7–8 Hz) for H in $(CF_3)_2CH$ is at about 4.4 ppm. The ^{19}F nmr shows a doublet around −1.3 to −2.3 ppm.

Use of excessively low temperatures for these reactions should be avoided, as polymer formation may ensue. Thus, adding the thioketene to ethanol at −80° results in 38% conversion to the thioketene polymer.[12]

Hydration.—To 10 ml of concentrated sulfuric acid containing an added 0.5 ml of water was added 5 g of the thioketene with stirring. The thioketene became decolorized in 5 min; 5 g more of the thioketene was added with cooling in ice. The mixture was poured onto ice and the fluoro acid was collected with dichloromethane. After drying ($MgSO_4$), distillation gave 7.3 g (67%) of 3,3,3-trifluoro-2-(trifluoromethyl)thiopropionic acid: bp 97–99°; $n^{25}D$ 1.3489; ir 2976 (CH), 2571 (SH), 1709 (C=O), 1330–1100 cm^{-1} (CF); ^1H nmr (neat) 4.05 [septuplet, $(CF_3)_2CH$], 5.02 ppm (s, SH).

Anal. Calcd for $C_4H_2F_6OS$: C, 22.65; H, 0.95; S, 15.12; neut equiv, 212. Found: C, 23.01; H, 1.06; S, 15.68; neut equiv, 214.

3,3,3-Trifluoro-2-(trifluoromethyl)thiopropionyl Bromide.—About 1.8 ml (4.9 g, 0.06 mol) of HBr was condensed into a glass tube cooled in Dry Ice–acetone and 5.82 g (0.03 mol) of bis(trifluoromethyl)thioketene was added. The tube was sealed and allowed to stand at 24° for 64 hr. Distillation gave 5.54 g (65%) of the purple thioacyl bromide: bp 94–96°; $n^{25}D$ *ca.* 1.401; ^1H nmr (neat) 4.65 ppm (septuplet); ^{19}F nmr −1.15 ppm (d, J = 6.8 Hz).

Anal. Calcd for C_4HBrF_6S: C, 17.47; H, 0.37; S, 11.66. Found: C, 17.85; H, 0.47; S, 11.36.

When triethylamine in dichloromethane was added to a solution of the product in dichloromethane, bis(trifluoromethyl)-thioketene dimer[1] was formed.

4-Amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline Product.—The imidazoline[4] 1 (1.79 g, 0.005 mol), 5 ml of benzene, and 2.14 g (0.011 mol) of bis(trifluoromethyl)thioketene were heated at 100° for 5 hr in a sealed glass tube. The benzene was evaporated and the product was recrystallized from dichloromethane to give 3.13 g (84%) of 4-{2-[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-4-[2,2,2-trifluoro-1-(trifluoromethyl)-ethylidene]-1,3-dithietan-2-ylamino}-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (2): mp 122.5–123°; ir 3472 (NH), 3021 (CH), 1681 (C=N), 1634 (C=C), 1565 cm^{-1} (NH deformation); ^1H nmr [$(CD_3)_2CO$] 6.29 [septuplet, J = 11 Hz, $(CF_3)_2CH$], 6.29 (s, NH), 9.14 ppm (s, broadened, NH); ^{19}F nmr −8.00 [s, $(CF_3)_2C{=}C$], −4.22 [d, J = 8 Hz, $(CF_3)_2CH$], +5.50, +10.8 (broadened peaks with evidence of splitting, one peak for each pair of ring CF_3 groups).

Anal. Calcd for $C_{15}H_3F_{24}N_3S_2$: C, 24.17; H, 0.41; S, 8.60. Found: C, 24.45; H, 0.61; S, 8.69.

No 1:1 adduct could be detected, even when excess imidazoline was used.

Reaction with 3-Methyl-1-*p*-tolyltriazene.—To 5.96 g (0.04 mol) of 3-methyl-1-*p*-tolyltriazene in 20 ml of dichloromethane was added 7.76 g (0.04 mol) of bis(trifluoromethyl)thioketene with stirring and cooling in ice. Nitrogen was evolved. Distillation gave 2.74 g (22%) of *p*-tolyl 3,3,3-trifluoro-2-(trifluoromethyl)-*N*-methylthiolpropionimidate, bp 61–63° (0.4 mm). Recrystallization from methanol left 2.02 g: mp 50–51.3°; ir 2976, 2899 (CH), 1629, 1493 (C=N and aromatic C=C), 846 cm^{-1} (para-disubstituted aromatic); ^1H nmr (CCl_4) 2.24 (s, CH_3 on phenyl), 3.26 (s, CH_3N), 3.71 [septuplet, $(CF_3)_2CH$], 7.71 ppm (A_2B_2 pattern, C_6H_4); ^{19}F nmr −2.57 ppm (d, J = 7 Hz).

Anal. Calcd for $C_{12}H_{11}F_6NS$: C, 45.71; H, 3.52; N, 4.44; S, 10.17. Found: C, 45.47; H, 3.73; N, 4.61; S, 10.16.

Hydrolysis with a hot solution of KOH in methanol–water resulted in the formation of *p*-toluenethiol, identified by odor, melting point, and mixture melting point (42°) and by comparison of nmr spectrum.

Reaction with 1,3-Di-*p*-tolyltriazine.—To 2.25 g (0.01 mol) of 1,3-di-*p*-tolyltriazene[13] in 10 ml of dichloromethane was added 1.94 g (0.01 mol) of bis(trifluoromethyl)thioketene. Nitrogen was slowly evolved. After 20 hr the solvent was removed under vacuum and the residue was steam distilled. The product was filtered off, dried, and recrystallized from methanol to give 1.3 g (33%) of *p*-tolyl 3,3,3-trifluoro-2-(trifluoromethyl)-*N*-*p*-tolylthiolpropionimidate: mp 67–67.5°; ir 3077, 3030 (=CH), 2976, 2915, 2857 (CH), 1639, 1623, 1506, 1493 (C=N and aromatic C=C), 854 cm^{-1} (para-disubstituted aromatic); ^1H nmr ($CDCl_3$) 2.32 (2 overlapping CH_3 peaks 0.02 ppm apart), 3.98 [septuplet, $(CF_3)_2CH$], 6.97, 7.25 ppm (centers of overlapping A_2B_2 patterns for two C_6H_4 groups); ^{19}F nmr −2.94 ppm (d, J = 7 Hz).

Anal. Calcd for $C_{18}H_{15}F_6NS$: C, 55.24; H, 3.86; S, 8.19. Found: C, 55.53; H, 3.91; S, 8.29.

Reaction with *N*,*N*-Dimethylanilines. A. *N*,*N*-Dimethylaniline.—*N*,*N*-Dimethylaniline (4.84 g, 0.04 mol) in 15 ml of petroleum ether (bp 30–60°) was stirred and cooled in ice and 7.76 g (0.04 mol) of bis(trifluoromethyl)thioketene was added dropwise. A reddish color developed with each drop and then faded. The crystals that separated were filtered off and rinsed with petroleum ether. Concentration of the mother liquor gave more for a total of 9.4 g (75%) of *N*-methyl-*N*-[3,3,3-trifluoro-2-(trifluoromethyl)propenylthiomethyl]aniline. Recrystallization from petroleum ether (18 ml) left 8.2 g: mp 51–52°; ir 3077 (=CH), 2959, 2915, 2857 (CH), 1608 [$(CF_3)_2C{=}C$], 1582, 1511, 1493 (aromatic C=C), 1408 cm^{-1} (NCH_3); ^1H nmr (CCl_4) 2.90 (s, CH_3), 4.87 (s, CH_2), 7.0 (m, C_6H_5), 7.45 ppm [quadruplet, J = 1.4 Hz, $(CF_3)_2C{=}CH$]; ^{19}F nmr −4.81, −6.92 ppm (quadruplets, components of former split to doublets, J = 1.4 Hz).

Anal. Calcd for $C_{12}H_{11}F_6NS$: C, 45.71; H, 3.52; S, 10.17. Found: C, 45.98; H, 3.72; S, 9.93.

The compound is stable at 4° but decomposes after several weeks at 24°. It is not basic enough to dissolve in aqueous hydrochloric acid but the hydrochloride was made by passing HCl into an ethereal solution of the amine, mp 103–106°.

Anal. Calcd for $C_{12}H_{11}F_6NS{\cdot}HCl$: Cl, 10.08. Found: Cl, 10.03.

B. *N*,*N*-Dimethyl-*p*-toluidine.—The thioketene (7.76 g, 0.04 mol) was added with cooling to 5.40 g (0.04 mol) of *N*,*N*-dimethyl-*p*-toluidine in 15 ml of dichloromethane. The product was distilled to give 4.76 g (36%) of *N*-methyl-*N*-[3,3,3-trifluoro-2-(trifluoromethyl)propenylthiomethyl]-*p*-toluidine: bp 60° (0.2 mm); $n^{25}D$ 1.5001; ^1H nmr (neat) 1.95 (s, *p*-CH_3), 2.47 (s, NCH_3), 4.37 (s, CH_2), 6.48 (A_2B_2 pattern, *p*-C_6H_4), 7.23 ppm [quadruplet, J = 1.4 Hz, $(CF_3)_2C{=}C$]; ^{19}F nmr −4.84, −7.15 ppm (quadruplets, components of former split to doublets).

(12) M. S. Raasch, U. S. Patent 3,275,609 (1966).

(13) P. Jacobson, *Justus Liebigs Ann. Chem.*, **427**, 152 (1922).

Anal. Calcd for $C_{13}H_{13}F_6NS$: C, 47.41; H, 3.98; S, 9.74. Found: C, 47.79; H, 4.24; S, 9.80.

C. *N,N*-Dimethyl-*m*-nitroaniline.—A solution of 0.03 mol of each of the reactants in 25 ml of dichloromethane was allowed to stand for 2 days, then extracted with 10% HCl to remove unreacted *N,N*-dimethyl-*m*-nitroaniline. The solution was evaporated on a steam bath to drive out the thioketene dimer. The residue was recrystallized from cyclohexane containing a little dichloromethane to give 3.76 g (35%) of *N*-methyl-3-nitro-*N*-[3,3,3-trifluoro-2-(trifluoromethyl)propenylthiomethyl]-aniline: mp 58°; ^{1}H nmr 3.13 (s, CH_3), 5.04 (s, CH_2), 6.8–7.8 ppm (m, =CH + C_6H_5).

Anal. Calcd for $C_{12}H_{10}F_6N_2O_2S$: C, 40.00; H, 2.80; S, 8.90. Found: C, 40.30; H, 3.12; S, 9.01.

D. *N,N,N′,N′*-Tetramethylbenzidine.—To a solution of 1.20 g (0.05 mol) of *N,N,N′,N′*-tetramethylbenzidine in 12 ml of dichloromethane was added 3.88 g (0.02 mol) of the thioketene with cooling in ice. Part way through the addition a product precipitated (monoadduct?) and then dissolved as addition continued. Evaporation of the solvent and recrystallization of the residue from cyclohexane gave 2.3 g (73%) of *N,N′*-bis[3,3,3-trifluoro-2-(trifluoromethyl)propenylthiomethyl]-*N,N′*-dimethylbenzidine: mp 132–132.5°; ^{1}H nmr ($CDCl_3$) 3.11 (s, CH_3), 5.09 (s, CH_2), 7.32 (aromatic A_2B_2 pattern), 7.67 ppm [quadruplet, J = 1.4 Hz, $(CF_3)_2C$=CH].

Anal. Calcd for $C_{24}H_{20}F_{12}N_2S_2$: C, 45.85; H, 3.21; S, 10.20. Found: C, 45.76; H, 3.37; S, 9.97.

Reaction with Ethers. A. Benzyl Methyl Ether.—To 6.10 g (0.05 mol) of freshly distilled benzyl methyl ether was added 6.79 g (0.035 mol) of the thioketene. After 16 hr at 24° the product was distilled to give 6.7 g (60%) of α-[3,3,3-trifluoro-2-(trifluoromethyl)propenylthio]benzyl methyl ether: bp 65° (0.2 mm); n^{25}D 1.4699; ir 3049 (=CH), 2941, 2841 (CH), 1623 (linear C=C), 1502 cm^{-1} (aromatic C=C); ^{1}H nmr (neat) 3.05 (s, CH_3), 5.19 (s, CH of benzyl), 6.95 (m, C_6H_5), 7.40 ppm [quadruplet, J = 1.4 Hz, $(CF_3)_2C$=CH]; ^{19}F nmr −6.51, −4.03 ppm (quadruplets, J = 7 Hz, components of latter split to doublets, J = 1.4 Hz).

Anal. Calcd for $C_{12}H_{10}F_6OS$: C, 45.56; H, 3.19; S, 10.14. Found: 45.12; H, 3.27; S, 10.52.

B. Ethyl Ether.—Bis(trifluoromethyl)thioketene (7 g) and 7 ml of ethyl ether were allowed to stand for 2 days. The solution was then cooled in ice and 3.24 g (46%) of the thioketene dimer[1] was filtered off. Distillation of the filtrate gave 2.33 g (24%) of ethyl 1-[3,3,3-trifluoro-2-(trifluoromethyl)propenylthio]ethyl ether, bp 70° (17 mm). The compound was purified for analysis by glpc over Triton X 305 (Rohm and Haas Co.) on diatomite: n^{25}D 1.3953; ir 3058 (=CH), 2985, 2941, 2899 (CH), 1616 (C=C), 1379 cm^{-1} (CCH_3); ^{1}H nmr (neat) 0.86 (t, CH_3CH_2), 1.27 (d, CH_3CH), 3.28 (AB part of ABX_3, CH_2), 4.53 (quadruplet, CH_3CH), 7.58 ppm [quadruplet, $(CF_3)_2C$=CH]; ^{19}F nmr −3.56, −5.82 ppm (quadruplets).

Anal. Calcd for $C_8H_{10}F_6OS$: C, 35.83; H, 3.76; S, 11.95. Found: C, 35.48; H, 4.02; S, 11.99.

A mixture, 0.62 g, bp 29–42° (0.12 mm), was also formed.

When run in the presence of 3 drops of 40% peracetic acid, the reaction was rapid but produced more of a mixture.

Reactions with Hydrides. A. Diethylsilane.—To 2.64 g (0.03 mol) of diethylsilane was added 5.82 g (0.03 mol) of bis(trifluoromethyl)thioketene with occasional cooling. After the color of the thioketene had disappeared, the product was cooled and 1.63 g of the thioketene dimer was filtered off. Distillation of the filtrate gave 2.14 g (25%) of diethyl[3,3,3-trifluoro-2-(trifluoromethyl)propenylthio]silane: bp 75–76° (16 mm); n^{25}D 1.4119; ^{1}H nmr (neat) 4.43 (broadened peak, SiH), 7.33 ppm [quadruplet for $(CF_3)_2C$=CH, J = 1.6 Hz]; ^{19}F nmr −3.05, −5.98 ppm (quadruplets, components of former split to doublets, J = 1.6 Hz).

Anal. Calcd for $C_8H_{12}F_6SSi$: C, 34.03; H, 4.29; S, 11.36. Found: C, 33.53; H, 4.09; S, 11.75.

B. Triethylsilane.—Addition of 5.82 g (0.03 mol) of the thioketene to 3.48 g (0.03 mol) of triethylsilane at 25–30° and distillation gave 6 g (64%) of triethyl[3,3,3-trifluoro-2-(trifluoromethyl)propenylthio]silane: bp 64° (28 mm); n^{25}D 1.4242; ir 2976, 2924, 2890 (CH), 1600 cm^{-1} (C=C); ^{1}H nmr 7.42 ppm [quadruplet, J = 1.6 Hz, $(CF_3)_2C$=CH]; ^{19}F nmr −3.25, −6.18 ppm (quadruplets, components of former split to doublets, J = 1.6 Hz).

Anal. Calcd for $C_{10}H_{16}F_6SSi$: C, 38.68; H, 5.20; S, 10.33. Found: C, 38.67; H, 5.00; S, 10.53.

C. Diphenylsilane.—Diphenylsilane (5.52 g, 0.03 mol) and 5.82 g (0.03 mol) of thioketene were allowed to stand for 16 hr. Distillation gave 3.75 g (33%) of diphenyl[3,3,3-trifluoro-2-(trifluoromethyl)propenylthio]silane: bp 92–94° (0.05 mm); n^{25}D 1.5226; ^{1}H nmr (neat) 5.10 (s, SiH), 6.6–7.2 ppm (m, C_6H_5 and -CH=); ^{19}F nmr −3.58, −6.72 ppm (quadruplets, components of former split to doublets, J = 1.6 Hz).

Anal. Calcd for $C_{16}H_{12}F_6SSi$: C, 50.78; H, 3.20; S, 8.47. Found: C, 51.04; H, 3.40; S, 8.32.

D. Triphenylstannane.—To a solution of 3.51 g (0.01 mol) of triphenylstannane in 10 ml of dichloromethane was added 2.04 g (0.0105 mol) of the thioketene. A white solid was filtered off and the solvent was removed from the filtrate, finally under vacuum. The residue crystallized after several days and was recrystallized from petroleum ether in several crops to give 2.95 g (54%) of triphenyl[3,3,3-trifluoro-2-(trifluoromethyl)propenylthio]stannane: mp 63–64°; ir 3058 (=CH), 1613 (olefinic C=C), 1585, 1570 (aromatic C=C), 730, 696 cm^{-1} (monosubstituted aromatic); ^{1}H nmr (CCl_4) =CH– peak in the aromatic multiplet at 7–7.7 ppm; ^{19}F nmr −4.38, −7.80 ppm (quadruplets, components of former split to doublets, J = 1.6 Hz).

Anal. Calcd for $C_{22}H_{16}F_6SSn$: C, 48.48; H, 2.96; S, 5.88. Found: C, 48.86; H, 3.07; S, 5.78.

Trimethylstannane.—To 4.95 g (0.03 mol) of trimethylstannane[14] in 10 ml of hexane was added, with cooling in ice, 5.82 g (0.03 mol) of the thioketene. The reaction was vigorous. The hexane was removed at 25° and 11 mm. The liquid compound was unstable to heat and deposited a solid on standing. However, an nmr spectrum taken immediately after removal of the hexane showed the compound to be trimethyl[3,3,3-trifluoro-2-(trifluoromethyl)propenylthio]stannane: ^{1}H nmr (neat) 0.47 (s, CH_3), 7.57 ppm [quadruplet, $(CF_3)_2C$=CH]; ^{19}F nmr −4.50, −7.40 ppm (quadruplets, components of former split to doublets).

Ene Reactions. A. General Conditions.—Where a temperature of 24° is indicated in Table II, bis(trifluoromethyl)-thioketene was added to the olefin while it was stirred and cooled in ice if necessary to hold the temperature down. The solution was then allowed to stand at room temperature. Reactions at 100° were run in sealed glass tubes. Structures were established by nmr. The $(CF_3)_2C$=CHS– group shows a characteristic quadruplet (J = 1.4 Hz) for H at 7.1–8.2 ppm. The ^{19}F nmr has a quadruplet (J = *ca.* 6.4 Hz) at −2.98 to −5.05 ppm with components split to doublets (J = 1.4 Hz) and a second, unsplit quadruplet at −5.20 to −7.35 ppm.

B. With 1,5-Cyclooctadiene.—In the reaction of the thioketene with 1,5-cyclooctadiene to produce mono- and diadducts (Table II), the first yields recorded were produced by using the reactants in the molar ratio of 1:1.1 while the second yields were obtained from a reactant ratio of 1:4. The structure of the diadduct is established by nmr by the presence of three ring -CH= groups rather than four.

C. With Cyclobutene.—Cyclobutene[15] (1.9 g, 0.035 mol), 5 ml of dichloromethane, and 7 g (0.036 mol) of the thioketene were sealed in a glass tube and heated at 100° for 1 hr. Distillation gave 2.38 g, bp 38–43° (2.2 mm), and 2.77 g, bp 51–61° (0.1 mm). Analytical glpc on the low boiler indicated a 71% component, but in preparative glpc over 20% fluoroalkyl pyromellitate on firebrick most of the product polymerized on the column. A small amount of material identified as CH_2=CHCH=CHS-CH=C$(CF_3)_2$, 1,3-butadienyl 3,3,3-trifluoro-2-(trifluoromethyl)-propenyl sulfide, was obtained: n^{25}D 1.4683; ir 3058 (=CH), 1605 (C=CS), 1570 cm^{-1} (conjugated diene); ^{1}H nmr (neat) 4.6–5.1 (m, CH_2=), 5.6–6.3 (m, 3 CH=), 7.17 ppm [quadruplet, J = 1.4 Hz, $(CF_3)_2C$=CH]; ^{19}F nmr −3.78, −6.28 ppm (quadruplets, J = 6.5 Hz, components of former split to doublets, J = 1.4 Hz).

Anal. Calcd for $C_8H_6F_6S$: C, 38.70; H, 2.44; S, 12.92. Found: C, 37.87; H, 2.78; S, 12.93.

The reaction mixture was not examined further.

Cycloheptatriene Adduct.—Bis(trifluoromethyl)thioketene (7.76 g, 0.04 mol) was added to 3.68 g (0.04 mol) of cycloheptatriene with stirring and occasional cooling. Distillation gave 8.4 g, bp 83–86° (2 mm). Recrystallization from methanol left 5.9 g (51%) of 5,5-bis(trifluoromethyl)-3-thiatetracyclo[4.4.-0.$0^{2,10}$.$0^{4,9}$]dec-7-ene (**3**): mp 70–70.6°; Raman 1613 cm^{-}

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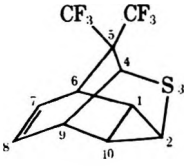
(15) J. D. Bacha and J. K. Kochi, *Tetrahedron*, **24**, 2215 (1968).

(C=C), ir 3049 (=CH), 2994 (CH), 1629, 1616 cm^{-1} (w, C=C); ^1H nmr ($CDCl_3$) (see positions below) 1.47 (quartet, 2-H), 1.94, 2.10 (m's, 1-H + 10-H), 3.26 (d with broadening, 4-H), 3.53 (tt, 9-H), 3.96 (peak broadened by CF_3's, 6-H), 6.20 (t, split to d, 8-H), 7.22 ppm (t, 7-H) (decoupling 7-H and 8-H affected 6-H and 9-H but not 4-H); ^{19}F nmr +2.20, −6.74 ppm [quadruplets, J = 12 Hz, former split to d, J = 2 Hz, positions show $(CF_3)_2C$=C not present].



Anal. Calcd for $C_{11}H_8F_6S$: C, 46.15; H, 2.82; S, 11.20. Found: C, 46.21; H, 2.88; S, 11.17.

(Methylthiomethyl)triphenylphosphonium Chloride.—Chloromethyl methyl sulfide[16] (33 g, 0.34 mol) and 90 g (0.34 mol) of triphenylphosphine were warmed together on a steam bath until the mixture solidified. Recrystallization from nitromethane gave 76 g (62%) of the salt in two crops, mp 219.5–220.5°.

Anal. Calcd for $C_{20}H_{20}ClPS$: C, 66.93; H, 5.62; S, 8.93. Found: 66.88; H, 5.82; S, 8.89.

Methyl 3,3,3-Trifluoro-2-(trifluoromethyl)propenyl Sulfide.—To 35.9 g (0.1 mol) of powdered (methylthiomethyl)triphenylphosphonium chloride suspended in 200 ml of tetrahydrofuran was added with stirring and cooling in ice 65 ml of 15% butyllithium in hexane (0.1 mol). Hexafluoroacetone was then passed in with continued cooling until there was no further evidence of reaction. All the liquid was distilled from the reaction mixture at 30 mm and collected in a Dry Ice trap. Fractionation gave a foreshot, bp 70–128.5°, and 8.3 g of the sulfide, bp 128.5°, $n^{25}D$ 1.3850. The foreshot was washed with water, dried, and distilled to give 3.9 g more of the sulfide, bp 127–128°, for a total yield of 58%: ir 3067 (=CH), 2950, 2857 (CH), 1608 (C=C), 1326 cm^{-1} (SCH_3); ^1H nmr (neat) 2.20 (s, CH_3), 7.48 ppm [quadruplet, J = 1.4 Hz, $(CF_3)_2C$=CH]; ^{19}F nmr −3.67, −6.11 ppm (quadruplets, J = 6.3 Hz, components of high field one split to doublets, J = 1.4 Hz).

Anal. Calcd for $C_5H_4F_6S$: C, 28.59; H, 1.92; S, 15.26. Found: C, 28.85; H, 2.18; S, 15.37.

(Benzylthiomethyl)triphenylphosphonium Chloride.—Benzyl chloromethyl sulfide[17] (45 g, 0.26 mol) and 69 g (0.26 mol) of triphenylphosphine were heated on a steam bath for 16 hr. The solid was broken up and washed with ether, yield 105 g (93%). The product was recrystallized from 315 ml of water to give 97 g (85%) of the salt in two crops, mp 216–217.5° after drying in air and under vacuum at 80°.

Anal. Calcd for $C_{26}H_{24}ClPS$: C, 71.79; H, 5.56; S, 7.37. Found: C, 71.92; H, 5.89; S, 7.40.

Benzyl 3,3,3-Trifluoro-2-(trifluoromethyl)propenyl Sulfide.—To 43.5 g (0.1 mol) of (benzylthiomethyl)triphenylphosphonium chloride suspended in 200 ml of tetrahydrofuran was added with cooling 70 ml (0.108 mol) of 15% butyllithium in hexane. Hexafluoroacetone was passed in, the solution was filtered, and the solvent was boiled off. Petroleum ether was added to the residue and the solid was filtered off. The filtrate was distilled to give 8.2 g (29%) of the sulfide: bp 117–119° (17 mm); $n^{25}D$ 1.4735; ^1H nmr (neat) 3.38 (s, CH_2), 6.83 (s, C_6H_5), 7.15 ppm [quadruplet, J = 1.4 Hz, $(CF_3)_2C$=CH]; ^{19}F nmr −4.28, −6.80 ppm (quadruplets, components of high field one split to doublets, J = 1.4 Hz).

Anal. Calcd for $C_{11}H_8F_6S$: C, 46.15; H, 2.82; S, 11.20. Found: C, 46.35; H, 3.12; S, 10.89.

(Phenylthiomethyl)triphenylphosphonium Chloride.—Chloromethyl phenyl sulfide[12] (64 g, 0.4 mol) and 105 g (0.4 mol) of triphenylphosphine were warmed on a steam bath for 45 min. The solid was washed with acetone to give 135 g (80%) of the phosphonium salt. Recrystallization from nitromethane gave 121 g (72%) in two crops, mp 232–234° dec.

Anal. Calcd for $C_{25}H_{22}ClPS$: C, 71.35; H, 5.27; S, 7.62. Found: C, 71.26; H, 5.42; S, 7.56.

Phenyl 3,3,3-Trifluoro-2-(trifluoromethyl)propenyl Sulfide.—The reaction and isolation were carried out on a 0.1-mol scale as described for the benzyl compound except that 65 ml of the butyllithium solution was used. Distillation gave 15.7 g (58%) of the sulfide: bp 107–108.5° (28 mm); $n^{25}D$ 1.4725; ^1H nmr (neat) 7.03 (s, C_6H_5), 7.33 ppm [quadruplet, J = 1.4 Hz, $(CF_3)_2$-C=CH]; ^{19}F nmr −4.05, −6.05 ppm (quadruplets, components of high field one split to doublets, J = 1.4 Hz).

Anal. Calcd for $C_{10}H_6F_6S$: C, 44.12; H, 2.22; S, 11.78. Found: C, 44.47; H, 2.44; S, 11.76.

Addition to Bicyclobutane.—The thioketene was added to an equivalent of bicyclobutane[18] in $CDCl_3$ at 0° and the nmr of the colorless solution was immediately taken: 2.50 (AB pattern, J = 14 Hz, high field pair split to m, low field pair split to d, J = 4 Hz, CH_2), 4.23 (broadened peak, CH), 4.30 (quadruplet, J_{H-CF_3} = 11 Hz, a notable value, SH), 5.75, 6.17 ppm (m's, CH=CH); ^{19}F nmr −8.93 (quintuplet, J = 11 Hz, formed by overlap of CF_3CF_3 and HCF_3 splittings of same J value), −12.0 ppm (quadruplet, $J_{CF_3CF_3}$ = 11 Hz). These data and the ir data in the discussion are consistent for 1-(3-cyclobutenyl)-3,3,3-trifluoro-2-(trifluoromethyl)-1-propenethiol (4).

The thioketene (14.4 g, 0.074 mol) was added to 4 g (0.074 mol) of bicyclobutane in 10 ml of dichloromethane at 0–5°. Vacuum flash distillation at room temperature of a portion into a Dry Ice trap caused the compound to turn purple. Distillation with a bath at 55–60° gave 8.2 g (45%) of purple liquid, bp 32–36° (3.5 mm), and a residue of 5.7 g of resin.

Anal. Calcd for $C_8H_4F_6S$: C, 38.70; H, 2.44; S, 12.92. Found: C, 38.26; H, 2.44; S, 12.88.

The ^1H nmr showed that some of the primary adduct was still present. A septuplet was present at 4.60 ppm [$(CF_3)_2CH$] and the CH=CH multiplets were largely replaced with a multiplet between them. A clean conversion of the primary adduct into 1,1,1-trifluoro-2-(trifluoromethyl)-4,6-heptadiene-3-thione (5) was thwarted because of concomitant polymerization.

Addition to Bicyclo[4.2.0]oct-7-ene.—Bis(trifluoromethyl)-thioketene (6.79 g, 0.035 mol) was added with stirring and cooling to 3.78 g (0.035 mol) of bicyclo[4.2.0]oct-7-ene.[19] The temperature was kept at about 25°: ^1H nmr of crude product (neat) 1.8–2.8 (multiple absorptions), 3.43 (s, fused CH nearest S), 5.22 (s, =CH of cyclobutene ring), 7.50 ppm [quadruplet, J = 1.4 Hz, $(CF_3)_2C$=CH]. These data indicate that the initial product is 7-[3,3,3-trifluoro-2-(trifluoromethyl)propenylthio]-bicyclo[4.2.0]oct-7-ene (6). Distillation gave 8 g (75%) of the isomerized product, 2-[3,3,3-trifluoro-2-(trifluoromethyl)propenylthio]-1,3-cyclooctadiene (7): bp 73° (0.06 mm); $n^{25}D$ 1.4982; ir 3067 (=CH), 2959, 2890, 2865 (CH), 1608 (substituent C=C), 1597 cm^{-1} (conjugated cyclic C=C); ^1H nmr (neat) 1.4, 1.85 (two peaks with splittings, 8 H, similar to saturated region of 1,3-cyclooctadiene spectrum), 5.98 (AB pattern, J = 15 Hz, CH=CH), 5.45 (overlapped peak for 3rd =CH), 7.32 ppm [quadruplet, J = 1.4 Hz, $(CF_3)_2C$=CH]; ^{19}F nmr −4.20, −6.63 ppm (quadruplets, J = 6.4 Hz, components of former split to doublets, J = 1.4 Hz).

Anal. Calcd for $C_{12}H_{12}F_6S$: C, 47.68; H, 4.00; S, 10.61. Found: C, 47.98; H, 4.04; S, 10.73.

Ozone was passed into 1.65 g of the compound in 35 ml of dichloromethane at −80°. The solution was allowed to warm to 24°, 4 ml of 30% hydrogen peroxide in 25 ml of acetic acid was added, and the mixture was warmed on a steam bath for 1 hr. Peroxide was destroyed by adding 5% Ru on C and the filtered solution was evaporated to dryness. The residue was rinsed with ether to leave 0.6 g (75%) of crude adipic acid, mp and mmp 152–153° after recrystallization from ethyl acetate.

Addition to Indole.—To 3.51 g (0.03 mol) of indole dissolved in 10 ml of chloroform was added 1.94 g (0.01 mol) of bis(trifluoromethyl)thioketene. After 16 hr the solution was cooled and filtered to give 1.81 g (58%) of red crystals of 2,2,2-trifluoro-1-(trifluoromethyl)ethyl-3-indolylthione: mp 199–200° after recrystallization from chloroform in 92% return; ir 3279 (NH), 3077 (=CH), 2933 (CH), 1610, 1585, 1506, 1490 (conjugated cyclic C=C), 754 cm^{-1} (ortho-disubstituted aromatic); ^1H nmr [$(CD_3)_2CO$] 5.41 [septuplet, $(CF_3)_2CH$], 6.2–7.1 (m, 3 H), 8.23 (d, proton in 2 position), 8.3–8.6 (m, 1 H), 11.10 ppm (broad, NH) (addition of D_2O caused the NH peak to disappear and the doublet at 8.23 ppm to be converted to a singlet); ^{19}F nmr (tetrahydropyran) −3.24 ppm (d, J = 7 Hz).

Anal. Calcd for $C_{12}H_7F_6NS$: C, 46.30; H, 2.27; S, 10.30. Found: C, 46.45; H, 2.36; S, 10.20.

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The compound in dichloromethane dissolved by reaction with another mole of the thioketene to form the unstable dithietane **8**. The product could be obtained in somewhat impure, pale yellow form by crystallization from the solvent: ir 3497 (NH), 3086 (=CH), 1618 (exocyclic C=C), 1534, 1490, 1477 cm^{-1} (cyclic, conjugated C=C); ^{19}F nmr (Me_2CO) −2.94 [d, $(CF_3)_2CH$], −7.71 ppm [s, $(CF_3)_2C=C$].

Addition to 1,3,3-Trimethyl-2-methyleneindoline.—To 5.19 g (0.03 mol) of 1,3,3-trimethyl-2-methyleneindoline (Eastman Kodak Co.) in 10 ml of dichloromethane, stirred and cooled in ice, was added 7.5 g (0.038 mol) of the thioketene at *ca.* 20°. Thioketene dimer was filtered off and the solvent was evaporated. The residue was recrystallized from methanol to give 5.87 g (53%) of orange 2,2,2-trifluoro-1-(trifluoromethyl)ethyl (1,3,3-trimethyl-2-indolinylidene)methylthione: mp 114–114.5°; ir 3030 (=CH), 2983, 2924 (CH), 1538, 1515, 1471 cm^{-1} (C=C); visible max (isooctane) 446 mμ (ε 29,920); uv max (isooctane) 253 mμ (ε 10,430); ^1H nmr (CCl_4) 1.44 [s, $(CH_3)_2C$], 3.42 (s, CH_3N), 4.42 [septuplet, $(CF_3)_2CH$], 6.42 (s, =CH), 7.17 ppm (m, 4 H, aromatic); ^{19}F nmr −2.55 ppm (d).

Anal. Calcd for $C_{16}H_{15}F_6NS$: C, 52.45; H, 4.13; S, 8.75. Found: C, 52.64; H, 4.09; S, 8.96.

Addition to 6-(Dimethylamino)fulvene.—To 6.05 g (0.05 mol) of 6-(dimethylamino)fulvene[20] in 35 ml of CCl_4 was added dropwise 9.70 g (0.05 mol) of the thioketene with stirring and cooling to keep the temperature at 25–30°. The product crystallized out and was filtered at 5° and rinsed with cold CCl_4. The product (6.6 g) was recrystallized from CCl_4 to give 5.9 g (37%) of purple 5-(dimethylaminomethylene)-1,3-cyclopentadien-1-yl-2,2,2-trifluoro-1-(trifluoromethyl)ethylthione: mp *ca.* 118° dec; ir 3067 (=CH), 2941 (CH), 1642, 1515 cm^{-1} (C=C); ^1H nmr (CD_3CN) 2.65 [s, $(CH_3)_2N$], 4.83 [septuplet, J = 8 Hz, $(CF_3)_2CH$], 5.70 (t, J = 4 Hz, H in 3 position) 6.32 (d, J = 4 Hz, H in 2 or 4 position), 6.52 (d, J = 4 Hz, H in 4 or 2 position), 8.26 ppm (septuplet, J = 0.7 Hz, exocyclic =CH); ^{19}F nmr −3.13 ppm (d, J = 8 Hz).

Anal. Calcd for $C_{12}H_{11}F_6NS$: C, 45.71; H, 3.52; S, 10.17. Found: C, 46.11; H, 3.64; S, 10.28.

Bis(trifluoromethyl)ketenimines.[21] **A. From Dimethylsulfur Diimide.**—To 2.7 g (0.03 mol) of dimethylsulfur diimide[22] in 5 ml of dichloromethane was added dropwise at 20° with stirring 11.64 g (0.06 mol) of bis(trifluoromethyl)thioketene. After 1 hr the volatile material was pulled off at 20 mm and caught in a Dry Ice trap. The pot was finally heated with steam. Fractionation gave 1.94 g (17%) of *N*-[3,3,3-trifluoro-2-(trifluoromethyl)-propenylidene]methylamine: bp 55–56° (184 mm); $n^{25}D$ 1.3345; ir 2967, 2899 (saturated CH), 2110 cm^{-1} (C=C=N); ^1H nmr (neat) 1.85 ppm (s); ^{19}F nmr −9.80 ppm (s).

Anal. Calcd for $C_5H_3F_6N$: C, 31.43; H, 1.58; N, 7.33. Found: C, 31.18; H, 1.83; N, 7.30.

B. From Di-*n*-butylsulfur Diimide.—The reaction was carried out with di-*n*-butylsulfur diimide[23] as described above. After 2 days, the volatile material was flashed into a Dry Ice trap at 1 mm. Distillation gave a 20% yield of the *n*-butylamine derivative: bp 75° (61 mm); $n^{25}D$ 1.3623; ir 2967, 2890 (saturated CH), 2114 cm^{-1} (C=C=N); ^{19}F nmr −10.1 ppm (s).

Anal. Calcd for $C_8H_9F_6N$: C, 41.20; H, 3.89; N, 6.01. Found: C, 41.12; H, 3.78; N, 5.80.

C. From Di-*tert*-butylsulfur Diimide.—The reaction was carried out with di-*tert*-butylsulfur diimide[24] as described under A. After 4 hr the product was distilled directly to give a 48% yield of the *tert*-butylamine derivative,[21,25] bp 66–68° (108 mm); $n^{25}D$ 1.3524; ir 2985 (saturated CH), 2096 cm^{-1} (C=C=N); uv max (isooctane) 268 mμ (ε 287); ^1H nmr (neat) 1.08 ppm (s); ^{19}F nmr −10.6 ppm (s).

Anal. Calcd for $C_8H_9F_6N$: C, 41.20; H, 3.89; N, 6.01. Found: C, 41.41; H, 4.17; N, 6.16.

D. From Diphenylsulfur Diimide.—The diphenylsulfur diimide was made by a modification of Cramer's procedure.[26] Aniline (56 g, 0.6 mol) in 100 ml of dichloromethane was cooled in Dry Ice–acetone and 11 g (0.1 mol) of sulfur tetrafluoride was passed in. The mixture was allowed to warm to 24° and the aniline hydrofluoride was filtered off. The solvent was boiled off, finally under vacuum on a steam bath. Petroleum ether was added to precipitate tar and the decanted solution was distilled to give 10.1 g (94%) of diphenylsulfur diimide, bp 105° (0.1 mm).

The reaction was carried out as under A and after 16 hr distillation gave a 38% yield of *N*-[3,3,3-trifluoro-2-(trifluoromethyl)propenylidene]aniline:[27] bp 60° (8 mm); ^1H nmr (neat) 6.75 ppm (m); ^{19}F nmr −10.2 ppm (s). Hydrolysis in warm, aqueous acetone gave $(CF_3)_2CHCONHC_6H_5$,[28] mp and mmp 171–172°.

Registry No.—**2,** 33830-86-3; **3,** 33872-36-5; **4,** 33830-87-4; **7,** 33830-88-5; 3,3,3-trifluoro-2-(trifluoromethyl)thiopropionic acid, 33830-89-6; 3,3,3-trifluoro-2-(trifluoromethyl)thiopropionyl bromide, 33830-90-9; *p*-tolyl 3,3,3-trifluoro-2-(trifluoromethyl)-*N*-methylthiolpropionimidate, 33830-91-0; *p*-tolyl 3,3,3-trifluoro-2-(trifluoromethyl)-*N*-*p*-tolylthiolpropionimidate, 33830-92-1; *N*-methyl-*N*-[3,3,3-trifluoro-2-(trifluoromethyl)propenylthiomethyl]aniline, 33890-40-3; 33830-93-2 (HCl); *N*-methyl-*N*-[3,3,3-trifluoro-2-(trifluoromethyl)propenylthiomethyl]-*p*-toluidine, 33830-94-3; *N*-methyl-3-nitro-*N*-[3,3,3-trifluoro-2-(trifluoromethyl)propenylthiomethyl]aniline, 33830-95-4; *N*,*N*′-bis[3,3,3-trifluoro-2-(trifluoromethyl)-propenylthiomethyl]-*N*,*N*′-dimethylbenzidine, 33830-96-5; α-[3,3,3-trifluoro-2-(trifluoromethyl)propenylthio]benzyl methyl ether, 33830-97-6; ethyl 1-[3,3,3-trifluoro-2-(trifluoromethyl)propenylthio]ethyl ether, 33830-98-7; triethyl[3,3,3-trifluoro-2-(trifluoromethyl)-propenylthio]silane, 33872-37-6; diphenyl[3,3,3-trifluoro-2-(trifluoromethyl)propenylthio]silane, 33830-99-8; triphenyl[3,3,3-trifluoro-2-(trifluoromethyl)propenylthio]stannane, 33831-00-4; $CH_2=CHCH=CHS-CH=C(CF_3)_2$, 33831-01-5; (methylthiomethyl)triphenylphosphonium chloride, 1779-54-0; methyl 3,3,3-trifluoro-2-(trifluoromethyl)propenyl sulfide, 33831-03-7; (benzylthiomethyl)triphenylphosphonium chloride, 33831-04-8; benzyl 3,3,3-trifluoro-2-(trifluoromethyl)propenyl sulfide, 33831-05-9; (phenylthiomethyl)triphenylphosphonium chloride, 13884-92-9; phenyl 3,3,3-trifluoro-2-(trifluoromethyl)propenyl sulfide, 33831-07-1; adipic acid, 124-04-9; 2,2,2-trifluoro-1-(trifluoromethyl)ethyl-3-indolylthione, 33831-08-2; 2,2,2-trifluoro-1-(trifluoromethyl)ethyl (1,3,3-trimethyl-2-indolinylidene)methylthione, 33831-09-3; 5-(dimethylaminomethylene)-1,3-cyclopentadien-1-yl-2,2,2-trifluoro-1-(trifluoromethyl)ethylthione, 33831-10-6; *N*-[3,3,3-trifluoro-2-(trifluoromethyl)propenylidene]methylamine, 23386-63-2; *N*-[3,3,3-trifluoro-2-(trifluoromethyl)propenylidene]-*n*-butylamine, 23386-64-3; *N*-[3,3,3-trifluoro-2-(trifluoromethyl)propenylidene]-*tert*-butylamine, 23409-78-1; diphenylsulfur diimide, 3839-89-2; *N*-[3,3,3-trifluoro-2-(trifluoromethyl)propenylidene]aniline, 1519-73-9; $(CF_3)_2CH-CONHC_6H_5$, 786-39-0; bis(trifluoromethyl)thioketene, 7445-60-5.

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Hydroxide Displacement of the Sulfone Linkage in Thioxanthen-9-one 10,10-Dioxides to Benzophenone-2′-hydroxy-2-sulfinic Acids. Intramolecular Cyclization to Xanthones

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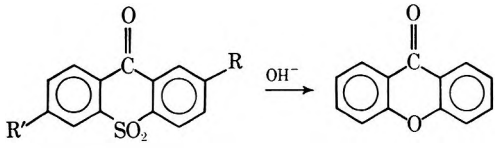
2-H, 2,6-diCOOH, 2-Cl, 2-CH_3, 2-CH_3O, and 2-NO_2 thioxanthen-9-one 10,10-dioxides were synthesized and treated, at reflux, with 2% NaOH–65% dioxane–H_2O. For these systems, facile hydroxide displacement of the sulfone linkage was found to occur exclusively on the more electrophilic ring to give the novel benzophenone-2′-hydroxy-2-sulfinic acids. Further, in alkaline media, these sulfinic acids generally undergo unique intramolecular cyclization to xanthones. The structures of the sulfinic acids were established by replacement of the sulfinic acid group with a chloromercury group followed by replacement of the latter with hydrogen to afford 2-hydroxybenzophenones.

Because thioxanthen-9-one 10,10-dioxides may possess some interesting physiologial properties, synthetic procedures leading to the preparation of a variety of substituted parent (**1**) systems have been reported.[3] Further, the well-known[4] colored solutions resulting from treatment of thioxanthen-9-one 10,10-dioxides with reducing agents in alkaline media have been investigated,[5] and epr data[6] have verified that formation of radical anions are responsible for the observed colors. While studying these color reactions in alkaline systems, the partial conversion of **1** to xanthone (**3**) was observed.[5a] Additional investigations relating to this transformation have not been reported and this interesting cleavage reaction has remained unexplained.



1, R = R′ = H
4, R = R′ = COOH

During the course of our recent studies[7] relating to the cyclization of diphenyl sulfone-2-carboxylic acids to thioxanthen-9-one 10,10-dioxides, we found that the heterocyclic moiety of the 2,6-dicarboxylic acid (**4**) of **1** was unstable to treatment with dilute aqueous sodium hydroxide. Since our results, along with those reported by Heymann, suggested a general lack of stability of the thioxanthen-9-one 10,10-dioxide nucleus in alkaline media, we undertook a more detailed investigation of this reaction system and report our findings in this paper.

For the purpose of this study, six thioxanthene-9-one 10,10-dioxides were prepared and refluxed with 2% sodium hydroxide–65% dioxane–water[8a] solution (Table I). All compounds underwent ring opening at the sulfone linkage[8b] under these conditions, and, following acidification, the corresponding novel hydroxybenzophenonesulfinic acids were obtained (Table II, A). In addition, except for the nitro compound **6**, xanthones were also isolated from the reaction mixtures (Table II, B). Nitro compound **6** gave only the 2′-hydroxy-5′-nitro-2-sulfinobenzophenone (**12**). Further, when the pure hydroxybenzophenonesulfinic acids were refluxed with 3% aqueous sodium hydroxide, all except **12** were converted to their corresponding xanthone products shown in Table III. Under these reaction conditions, the refractory nitro compound, **12**, remained unchanged even after reflux for 48 hr. The

TABLE I

THIOXANTHEN-9-ONE 10,10-DIOXIDES REACTED AT REFLUX IN 2% SODIUM HYDROXIDE–65% DIOXANE–H_2O

Reactant	mmol[a]	R′	R	Reaction time, hr	% Unreacted
1	16	H	H	4	61.5
4	6	COOH	COOH	0.25[b]	45.0
				5	7.5
5	14	H	Cl	4	50.2
6	14	H	NO_2	2	0.0
7	15	H	CH_3	18	23.0
8	15	H	CH_3O	18	28.8

[a] All reactions were run in 500 ml of solution except **4** which was run in 50 ml. [b] Yields in Table II were obtained for this reaction time.

(1) This investigation was supported in part by a National Science Foundation Undergraduate Research Grant No. GE 8888.

(2) (a) Taken in part from the M.S. theses of M. J. B. and R. M.; (b) the senior thesis of P. D.; (c) the Ph.D. dissertation of G. S.

(3) (a) E. D. Amstutz and C. R. Neumoyer, *J. Amer. Chem. Soc.*, **69**, 1925 (1947); (b) J. Blanz and F. A. French, *J. Med. Chem.*, **6**, 185 (1963).

(4) (a) C. Graebe and O. Schultheiss, *Justus Liebigs Ann. Chem.*, **263**, 10 (1891); (b) F. Ullmann and O. Von Glenck, *Ber.*, **49**, 2509 (1916); (c) E. D. Amstutz, E. A. Fehnel, and I. M. Hunsberger, *J. Amer. Chem. Soc.*, **70**, 133 (1948).

(5) (a) H. Heymann, *J. Amer. Chem. Soc.*, **71**, 260 (1949); (b) E. A. Fehnel, *ibid.*, **71**, 1065 (1949).

(6) E. T. Kaiser and L. Kevan, Ed., "Radical Ions," Interscience, New York, N. Y., 1968, Chapter 8, and references cited therein.

(7) O. F. Bennett and P. Gauvin, *J. Org. Chem.*, **34**, 4165 (1969).

(8) (a) All of the thioxanthen-9-one 10,10-dioxides were completely soluble in this solvent system, while many exhibited limited solubility in only aqueous hydroxide. (b) One referee of this manuscript has observed base-induced ring opening of the thioxanthen-9-one (**2**) ring system using Huang-Minlon conditions. Unlike the sulfone systems, he reports that ring opening in the sulfides does not lead to new, ring-closed products.

TABLE II

PRODUCTS OBTAINED FROM REACTION OF THIOXANTHEN-9-ONE 10,10-DIOXIDES[f]

A

Reactant	Benzophenone product[a] (yield, %)	Product	Mp, °C
1	2'-OH-2-SO_2H (25.1)	9	119–120
4	4,5'-diCOOH-2'-OH-2-SO_2H (40.0)	10	189–191
5	5'-Cl-2'-OH-2-SO_2H (37.0)	11	118–119
6	2'-OH-5'-NO_2-2-SO_2H (89.5)	12	123–124
7	2'-OH-5-CH_3-2-SO_2H (72.4)	13	123–124
8	2'-OH-5-CH_3O-2-SO_2H (68.1)	14	105–106

B

Reactant	Xanthone product (yield, %)	Product	Mp, °C
1	Xanthone[b] (13.4)	3	174–175
4	2,6-diCOOH[c] (15.0)	15	407–412
5	2-Cl[b] (13.3)	16	170–171
7	2-CH_3[b,d] (4.6)	17	121–122
8	2-CH_3O[b,e] (3.1)	18	134–135

[a] Products 10 and 11 were purified by crystallization from aqueous methanol. All other products were crystallized from aqueous acetone. [b] Infrared and melting point comparisons with authentic samples were identical. [c] Infrared and melting point comparisons made with a sample prepared by an independent procedure proved identity; see Experimental Section. [d] F. Ulmann and M. Slokasow, *Ber.*, **38**, 2115 (1905). [e] A. Baeyer, *Justus Liebigs Ann. Chem.*, **372**, 102 (1910). [f] Satisfactory analytical values (±0.4% for C, H, S) for all new compounds were reported: Ed.

TABLE III

CYCLIZATION OF THE HYDROXYBENZOPHENONESULFINIC ACIDS TO XANTHONES BY REFLUX IN 3% AQUEOUS SODIUM HYDROXIDE

Reactant	mmol	Reaction time, hr	% Unreacted	Xanthone product	Yield, %
9	2	2	26.8	3	73.2
10	1.4	2	37.0	15	63.0
11	2	2	47.2	16	52.8
12	2	48	100.0		0.0
13	2	4	76.4	17	23.6
13	2	40	18.8	17	81.2
14	2	4	82.0	18	18.0
14	2	40	33.0	18	67.0

TABLE IV

PREPARATION OF HYDROXYCHLOROMERCURIBENZOPHENONES FROM THE HYDROXYBENZOPHENONESULFINIC ACIDS[b]

Reactant	mmol	Chloromercuri product[a] (yield, %)	Product	Mp, °C
9	15	2'-HgCl-2-OH (69.6)	19	185–187
10	3	2'-HgCl-4',5-diCOOH-2-OH (70.3)	20	304–306 dec
11	13	5-Cl-2'-HgCl-2-OH (74.6)	21	206–208
12	13	2'-HgCl-2-OH-5-NO_2 (82.1)	22	255–256
13	14	2-HgCl-2'-OH-5-CH_3 (74.7)	23	203–204
14	14	2-HgCl-2'-OH-5-CH_3O (68.2)	24	203–204

[a] All products were purified by crystallization from aqueous acetone [b] Satisfactory analytical values (±0.4% for C, H) for all compounds were reported: Ed.

TABLE V

o-HYDROXYBENZOPHENONES FROM THE HYDROXYCHLOROMERCURIBENZOPHENONES[e]

Reactant	mmol	*o*-Hydroxy product (yield, %)	Product	Mp, °C	Recrystn solvent
19	18	2-OH[a] (91.8)	25	38–39	Distilled bp 136–138° (1.9 mm)
20	19	4',5-diCOOH-2-OH[b] (89.0)	26	334–336 dec	Aqueous acetone
21	16	5-Cl-2-OH[b] (84.9)	27	93–94	Ethanol
22	16	2-OH-5-NO_2[c] (84.0)	28	123–124	Ethanol
23	15	2-OH-3'-CH_3[d] (82.4)	29	Liquid	Distilled, bp 140–141° (0.9 mm)
24	15	2-OH-3'-CH_3O[d] (83.6)	30	Liquid	Distilled, bp 148–149° (0.5 mm)

[a] The solid oxime was prepared, mp 132–134° [lit. mp 135°: E. P. Kohler and W. F. Bruce, *J. Amer. Chem. Soc.*, **53**, 1572 (1931)]. [b] Comparison made to Sadtler Research Laboratories, Standard Infrared Spectra, Grating 24374. [c] See F. Ulmann and J. H. Mallet, *Ber.*, **31**, 1696 (1898). [d] Comparisons made to structures prepared by independent procedures proved identity; see Experimental Section. [e] Satisfactory analytical values (±0.4% for C, H) for all compounds except 19, 21, and 22 were reported: Ed.

xanthone structures were confirmed by elemental analysis and by infrared and melting point comparison to known compounds. The structure of the new diacid xanthone, **15**, was established by comparison to a sample synthesized by an independent route (see Experimental Section).

All of the hydroxybenzophenonesulfinic acids immediately decolorize cold neutral permanganate and also give a positive Krishna test[9] indicating the presence of a sulfinic acid group. Their general structures were consistent with elemental analyses (Table II) as well as with ir and nmr data, but their absolute structures were established by synthetic procedures. Thus, for each hydroxybenzophenonesulfinic acid, the sulfinic acid group was replaced by a chloromercury group[10] to afford the corresponding solid hydroxychloromercuribenzophenones (Table IV). Removal of the chloromercury group was achieved in acid solution to give the respective 2-hydroxybenzophenones (Table V) which were compared to known compounds or to structures synthesized by independent methods.

The reported[5a] finding of xanthone product following treatment of thioxanthen-9-one 10,10-dioxide in alkaline media can now be explained as the result of nucleophilic displacement of the sulfonyl linkage in the thioxanthen-9-one 10,10-dioxide moiety leading to the novel hydroxybenzophenonesulfinic acids. Further, in alkaline systems, the unique functionality of these sulfinic acids allows intramolecular displacement of the sulfinate group to afford xanthone products. Failure of the nitro compound **12** to undergo cyclization reaction may be attributable to the reduced nucleophilic strength of the phenoxy anion due to the strong electron-withdrawing influence of the *p*-nitro substituent.

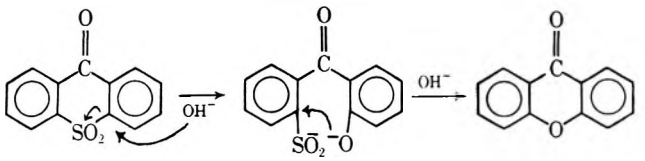
Although for a given substituted thioxanthen-9-one 10,10-dioxide, two isomeric cleavage products are theoretically possible, we found no evidence to indicate that displacement reaction occurred other than exclusively on the more electrophilic aromatic ring.

Scheme I proposes a general mechanism that is con-

(9) S. Krishna and H. Singh, *J. Amer. Chem. Soc.*, **50**, 792 (1928).

(10) (a) W. Peters, *Ber.*, **38**, 2567 (1905). (b) I. L. Finar, "Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1955, p 522.

SCHEME I



sistent with the cleavage–cyclization reactions found in this investigation. Although some inorganic sulfite results from the cyclization reaction, the precise nature of the sulfinate displacement is not presently known.

Experimental Section[11]

Preparation of the Thioxanthen-9-one 10,10-Dioxides (1, 4–8).—The reported procedure[4b] for the oxidation of thioxanthen-9-one and 2-chlorothioxanthen-9-one in hydrogen peroxide (30%) and glacial acetic acid gave thioxanthen-9-one 10,10-dioxide[4b] (1) (84%) and 2-chlorothioxanthen-9-one 10,10-dioxide[12] (5) (85%). Thioxanthen-9-one 10,10-dioxide-2,6-dicarboxylic acid (4) was prepared (85%) according to the cyclization procedure reported by Bennett and Gauvin.[7] The condensation procedure reported by Roberts and Smiles[13] was utilized to obtain the 4′-nitro-[14] (72%), 4′-methyl-[15] (70%), and 4′-methoxydiphenyl sulfide-2-carboxylic acids[13] (78%). Cyclization of the 4′-methyl and the 4′-methoxydiphenyl sulfide-2-carboxylic acids was achieved in concentrated sulfuric acid at 100° and 50°, respectively, to afford 2-methylthioxanthen-9-one[16] (79%) and 2-methoxythioxanthen-9-one[17] (84%). The cyclization of 4′-nitrodiphenyl sulfide-2-carboxylic acid to 2-nitrothioxanthen-9-one (47%) was effected using the procedure of Mayer,[14] which involved reaction of the acid chloride with aluminum chloride. The oxidation of the 2-nitro-, 2-methyl-, and 2-methoxythioxanthen-9-ones in hydrogen peroxide and glacial acetic acid afforded the 2-nitro-[14] (6) (89%), 2-methyl-[18] (7) (70%), and 2-methoxythioxanthen-9-one 10,10-dioxides[19] (8) (73%).

All compounds synthesized were identified by satisfactory elemental analyses, melting points, and ir and nmr data.

Reaction of the Thioxanthen-9-one 10,10-Dioxides in 2% Sodium Hydroxide–65% Dioxane–Water.—The following typical examples illustrate the general procedures used to carry out the cleavage reactions. For each specific compound, changes in these procedures, as well as necessary product information, are noted in Tables I and II.

A. Reaction of Thioxanthen-9-one 10,10-Dioxide-2,6-dicarboxylic Acid (4).—In a typical reaction, 4 (2 g, 6 mmol) in 50 ml of 2% sodium hydroxide–65% dioxane–water was refluxed for 5 hr. The initial brown solution changed to a deep green as reflux began and this color persisted for 1 hr during the reaction time. Following addition of 150 ml of water, the dioxane was flash distilled and the cold, brown solution was acidified with 10% hydrochloric acid and filtered. The tan solid was washed with water, dried, and extracted with three 150-ml portions of cold acetone. The acetone-insoluble material, 1.56 g (92%), was identified as xanthone-2,6-dicarboxylic acid, 15 (Table II, B), by ir and melting point comparisons with a sample prepared by independent synthesis (*vide infra*).

The combined acetone extracts were evaporated to dryness, leaving 0.45 g of yellow powder. This solid was extracted with three 75-ml portions of ether, which left 0.15 g (7.5%) of unreacted 4. Evaporation of the ether extracts afforded 0.29 g of 4,5′-diearboxy-2′-hydroxy-2-sulfinobenzophenone, 10 (Table II, A).

B. Reaction of 2-Chlorothioxanthen-9-one 10,10 Dioxide (5).—A solution of 5 (4 g, 14 mmol) in 500 ml of 2% sodium hydroxide–65% dioxane–water was refluxed for 4 hr. The initial clear solution changed to a deep green as reflux began and this color persisted during the entire reaction time. Following the addition of 300 ml of water, the dioxane was removed by flash distillation and the solution was filtered. The white solid was washed with water, dried, and extracted with three 150-ml portions of cold ether. The ether-insoluble material, 1.99 g (50.2%), was unreacted 5. The combined ether extracts were evaporated to dryness, leaving 0.45 g of white solid. Crystallization from methanol gave 2-chloroxanthone, 16, which was identified by ir and melting point comparisons (Table II, B).

The remaining basic reaction solution was acidified with 10% hydrochloric acid to give a cloudy solution which was extracted with four 100-ml portions of cold ether. Evaporation of the ether extracts left a yellow oil which solidified on chilling to a light yellow solid. Two crystallizations from aqueous methanol afforded the white needles, 1.42 g, of 5′-chloro-2′-hydroxy-2-sulfinobenzophenone, 11 (Table II, A).

Cyclization of the Hydroxybenzophenonesulfinic Acids to Xanthones (Table III).—In a typical reaction, 0.5 g (2 mmol) of 13 was dissolved in 50 ml of 3% aqueous sodium hydroxide. The light yellow solution was refluxed for 4 hr with no color change. The white solid that formed was filtered from the cold solution, washed with water, and dried. This solid, 0.09 g, was 2-methylxanthone, 17, as shown by ir and melting point comparison with an authentic sample. The remaining basic solution was acidified with 10% hydrochloric acid and filtered. The solid, 0.38 g, was washed with water and dried, and was shown to be unreacted 13.

Preparation of Hydroxychloromercuribenzophenones from the Hydroxybenzophenonesulfinic Acids (Table IV).—The general procedure[10a] employed for the replacement of a sulfinic acid group with a chloromercury group was utilized in these preparations. In a typical reaction, 4 g (14 mmol) of 14, 12 g (44 mmol) of mercuric chloride, and 80 ml of water were added to 80 ml of glacial acetic acid. The mixture was heated to reflux, giving a light yellow solution as 14 dissolved. After a 4-hr reflux period, the solid precipitate was filtered from the cold solution, washed with water, and dried. Crystallization from acetone afforded yellow needles (4.3 g) of 2-chloromercuri-2′-hydroxy-5-methoxybenzophenone, 24.

Preparation of o-Hydroxybenzophenones from the Hydroxychloromercuribenzophenones (Table V).—The general procedure[20] employed for the replacement of a chloromercury group with hydrogen was utilized in these preparations. In a typical reaction, 8 g (16 mmol) of 22 and 200 ml of 95% ethanol was added to 200 ml of concentrated hydrochloric acid. The mixture was heated to reflux and after 2 hr a clear solution resulted. After 2 hr more at reflux, 300 ml of water was added to the cold solution and the ethanol was removed by flash distillation. The resulting acidic solution was extracted with five 100-ml portions of benzene and the benzene extracts were dried over anhydrous calcium carbonate. Evaporation of the benzene left 3.4 g of light tan solid. Crystallization from ethanol gave light tan needles of the known[21] 2-hydroxy-5-nitrobenzophenone, 28.

Synthesis of Xanthone-2,6-dicarboxylic Acid (15). General.—Starting with 2-chloro-4-methylaniline, the reported procedure of Goldberg and Wragg[22] was used to prepare 3-chloro-4-cyanotoluene in 45% yield. This product was converted to 2-chloro-4-methylbenzoic acid, following the literature procedure,[22] in 86% yield. Reaction of the benzoic acid product with *p*-cresol using the method of Kobrich[23] gave the known 2-carboxy-4′,5-dimethyldiphenyl ether (75%).

A. Diphenyl Ether-2,4′,5-tricarboxylic Acid (31).—2-Carboxy-4′,5-dimethyldiphenyl ether, 0.5 g (2 mmol), was refluxed for 5 hr in 125 ml of water containing 2.2 g (14 mmol) of potassium permanganate. The cold reaction mixture was filtered and the purple filtrate was acidified with 5% hydrochloric acid. The solid, obtained by filtration, was washed with water, dried, and crystallized from aqueous methanol to give 0.45 g (72%) of white 31, mp 314–318° dec.

Anal. Calcd for $C_{15}H_{10}O_7$: C, 59.58; H, 3.34. Found: C, 59.78; H, 3.32.

B. Xanthone-2,6-dicarboxylic Acid (15).—A stirred solution of 31 (0.2 g, 0.7 mmol) in 20 ml of concentrated sulfuric acid

(11) Melting points are corrected except for those compounds melting above 300°. Elemental analyses were performed by Dr. Carol K. Fitz, Needham Heights, Mass., and by Galbraith Laboratories, Inc., Knoxville, Tenn.

(12) H. Gilman and J. W. Diehl, *J. Org. Chem.*, **24**, 1914 (1959).

(13) K. C. Roberts and S. Smiles, *J. Chem. Soc.*, 867 (1929).

(14) F. Mayer, *Ber.*, **42**, 3050 (1909).

(15) J. Goldberg, *ibid.*, **37**, 4527 (1904).

(16) F. Mayer, *ibid.*, **43**, 588 (1910).

(17) W. G. Prescott and S. Smiles, *J. Chem. Soc.*, 645 (1911).

(18) F. Ulmann and A. Lehner, *Ber.*, **38**, 741 (1905).

(19) W. B. Price and S. Smiles, *J. Chem. Soc.*, 3159 (1928).

(20) T. Okamoto and J. F. Bunnett, *J. Amer. Chem. Soc.*, **78**, 5361 (1956).

(21) F. Ulmann and J. H. Mallet, *Ber.*, **31**, 1696 (1898).

(22) A. A. Goldberg and A. H. Wragg, *J. Chem. Soc.*, 4227 (1958).

(23) V. G. Kobrich, *Justus Liebigs Ann. Chem.*, **664**, 88 (1963).

was heated at 135° for 3 hr. The cool solution was poured onto ice and the solid, collected by filtration, was washed with water and several portions of hot methanol. The dry solid **15**, 0.15 g, was obtained in 83% yield, mp 407–412° dec, and was identical with the xanthone product obtained from cleavage of **4** (Table II, B) as shown by ir and melting point comparisons.

C. Dimethyl Xanthone-2,6-dicarboxylate (32).—Normal esterification of **15** could not be achieved due to its extreme insolubility. However, treatment of **15** with ethereal diazomethane gave **32**, mp 213–214°, from methanol. Similar treatment of **15** obtained from cleavage of **4** also afforded **32**.

Anal. Calcd for $C_{17}H_{12}O_6$: C, 65.38; H, 3.87. Found: C, 65.10; H, 3.80.

Synthesis of 2-Hydroxy-3′-methylbenzophenone (29).—The position of hydroxide displacement of the sulfone linkage in compounds **1**, **5**, and **6** was established by ultimate conversion of cleavage products **9**, **11**, and **12** to the known *o*-hydroxybenzophenones **25**, **27**, and **28**, respectively. Similar conversion of cleavage products **10**, **13**, and **14** led to the unknown *o*-hydroxybenzophenones, **26**, **29**, and **30**. Thus, for comparative purposes, these latter compounds were prepared by independent procedures.

Nakazawa and Baba[24] have reported on the Fries rearrangement of *m*-phenyltoluate to obtain 4-hydroxy-3′-methylbenzophenone. Utilizing their procedure, we have also isolated the 2-hydroxy isomer, **29**, from the reaction mixture.

To a stirred mixture of 26.6 g (0.2 mol) of aluminum chloride in 200 ml of carbon disulfide was added 23.2 g (0.1 mol) of *m*-phenyltoluate in 50 ml of carbon disulfide at a rate sufficient to promote solvent reflux. Following complete addition, reflux was continued for 2 hr before distillation of the carbon disulfide. The remaining reaction mixture was heated at 150° for 3 hr, cooled, and treated with 200 ml of cold 5% hydrochloric acid. Filtration gave the known 4-hydroxy-3′-methylbenzophenone,[24] mp 165–166°. The oily filtrate was extracted with four 100-ml portions of ether. Distillation gave 4.7 g of light yellow oil, bp 142–144° (1 mm).

Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.38; H, 5.80.

Ir and nmr comparison of this compound with **29** showed the two to be identical.

2-Methoxy-3′-methylbenzophenone (33).—To a stirred solution of 50 ml of water, 50 ml of acetone, and 0.68 g (17 mmol) of sodium hydroxide was added 4 g (17 mmol) of **29**. After reflux for 30 min, 16.3 g (28 mmol) of iodomethane dissolved in 50 ml of acetone was added slowly to the hot solution. Following reflux for 8 hr, the acetone and unreacted iodomethane were removed by flash distillation and the solution was acidified with 10% hydrochloric acid. The oily solution was extracted with four 100-ml portions of ether and dried ($MgSO_4$). Distillation gave 3.1 g of light yellow oil, **33**, bp 161–162° (0.8 mm).

Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.64; H, 6.24. Found: C, 79.37; H, 6.15.

Synthesis of 2-Hydroxy-3′-methoxybenzophenone (30).—In similar manner to that described above for the synthesis of **29**, Nakazawa and Baba[24] prepared 4-hydroxy-3′-methoxybenzophenone by the Fries rearrangement of *m*-phenylanisate. Utilizing their procedure we also isolated the 2-hydroxy isomer, **30**, from the reaction mixture. Thus, the Fries rearrangement was conducted as described above to the point where the reaction mixture was treated with cold 5% hydrochloric acid. The waxy solid which formed was removed by extraction with four 100-ml portions of ether. The ether solution was extracted with three 50-ml portions of 10% sodium hydroxide. Acidification of the basic extracts afforded the known 4-hydroxy-3′-methoxybenzophenone,[24] mp 137–138°, from methanol. Distillation of the remaining ether solution gave 7.2 g of light yellow oil, bp 148–150° (0.4 mm).

Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.69; H, 5.30. Found: C, 73.65; H, 5.40.

Ir and nmr comparison of this compound with **30** showed the two to be identical.

2,3′-Dimethoxybenzophenone (34).—Following the procedure used for the preparation of **33** afforded **34** as a light orange oil, bp 151–152° (0.35 mm). This oil solidified upon chilling, mp 27–28°.

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.38; H, 5.82. Found: C, 74.55; H, 5.91.

Conversion of 2-Hydroxybenzophenone-4′,5-dicarboxylic Acid (26) to 2-Methoxybenzophenone-4′,5-dicarboxylic Acid (35).—This methyl ether was prepared using the same general procedure that afforded methyl ethers **33** and **34**. Solid **35** was obtained in 70% yield, mp 306–309° dec, from aqueous methanol.

Anal. Calcd for $C_{16}H_{12}O_6$: C, 64.22; H, 3.71. Found: C, 63.87; H, 3.95.

2-Methoxydimethylbenzophenone-4′,5-dicarboxylate (36).—Treatment of **35** with ethereal diazomethane gave **36**, mp 138–139°, from aqueous methanol.

Anal. Calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.87. Found: C, 65.70; H, 4.90.

Synthesis of 2-Methoxybenzophenone-4′,5-dicarboxylic Acid (35). A. 2-Methoxy-4′,5-dimethylbenzophenone (37).—The reported[25] synthesis of 2-hydroxy-4′,5-dimethylbenzophenone was used to obtain this compound in 78% yield. Its methyl ether was prepared using the same general procedure that gave methyl ethers **33**, **34**, and **35**. Solid **37** was obtained in 72% yield, mp 81–82°, from aqueous methanol.

Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.00; H, 6.80.

B. Oxidation of 37 to 35.—A stirred mixture of **37** (1.4 g, 5.8 mmol), 7.7 g (43 mmol) of potassium permanganate, and 100 ml of 2% sodium hydroxide were heated at reflux for 3 hr and filtered. The cooled filtrate was acidified with dilute sulfuric acid, and 10% sodium bisulfite was added until the dark solution became clear. The solid was filtered, washed with dilute sulfuric acid and water, and dried. This product, 1.12 g (64%), was shown to be identical with **35** by melting point and ir comparisons. Further, diazomethane esterification of this compound gave **36**.

Registry No.—**3**, 90-47-1; **9**, 33886-18-9; **10**, 33785-48-7; **11**, 33785-49-8; **12**, 33785-50-1; **13**, 33785-51-2; **14**, 33785-52-3; **15**, 33872-64-9; **16**, 13210-15-6; **17**, 6280-45-1; **18**, 1214-20-6; **19**, 33785-56-7; **20**, 33785-57-8; **21**, 33785-58-9; **22**, 33785-59-0; **23**, 33785-60-3; **24**, 33785-61-4; **25**, 117-99-7; **26**, 33785-63-6; **27**, 85-19-8; **28**, 18803-19-5; **29**, 33785-66-9; **30**, 21554-73-4; **31**, 33785-68-1; **32**, 33785-69-2; **33**, 33785-70-5; **34**, 21554-74-5; **35**, 33785-72-7; **36**, 33785-73-8; **37**, 33785-74-9.

Acknowledgment.—We wish to thank Mr. James Johnson and Mr. Thomas Cigas for conducting several of the literature preparations.

(24) K. Nakazawa and S. Baba, *J. Pharm. Soc. Jap.*, **75**, 379 (1955).

(25) R. L. Shriner and R. B. Moffet, *J. Amer. Chem. Soc.*, **63**, 1967 (1941)

Sulfurization of Isocyanides[1]

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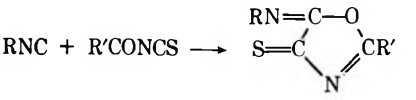
Both direct combination with elemental sulfur and reversible transfer of sulfur from an isothiocyanate transformed each of nine aryl isocyanides into the corresponding isothiocyanate. An equimolar mixture of phenyl isocyanide and phenyl isothiocyanate reacted with water in the presence of acid to form thiooxanilide in low yield.

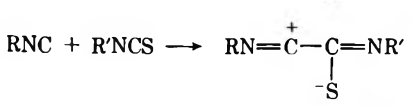
Sulfur transformed carbon monoxide in the presence of sodium acetate into carbon oxysulfide[2] and an isocyanide into an isothiocyanate.[3] Known for over a century this carbenoid reaction of an isocyanide has received little attention. The isocyano carbon also combined with selenium[3c] but failed to combine with either oxygen (without a catalyst)[4] or tellurium.[3c] Apparently these are reactions at nucleophilic isocyano carbon, $RN^+{\equiv}C:^-$.[5] A similar addition of sulfur to nucleophilic carbenes has been reported for diamino carbenes, $(R_2N)_2C:$[6a] and considered for diphenyl carbene, $(C_6H_5)_2C:$;[6b] however, an explanation for the formation of a thioketone based on initial dissociation of a tetraaminoethylene into a diaminocarbene followed by addition to sulfur[6a] has been challenged and replaced with one which calls for an initial attack on the π-electron system of the tetraaminoethylene.[6c]

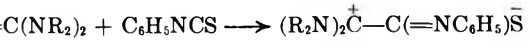
$$(R_2N)_2C{=}C(NR_2)_2 \overset{?}{\rightleftharpoons} (R_2N)_2C:$$

$$(R_2N)_2C{=}C(NR_2)_2 \xrightarrow{S} (R_2N)_2C{=}S$$

A nucleophilic attack by an isocyano carbon may occur in the [4 + 1] addition of an isocyanide to an acyl isothiocyanate,[7] and a similar, but previously unknown, attack by isocyano carbon upon a monofunctional isothiocyanate would be expected to lead initially to a zwitterionic adduct. A comparable adduct of a diamino carbene has been obtained from the dimer, a tetraaminoethylene, and phenyl isothiocyanate.[8]



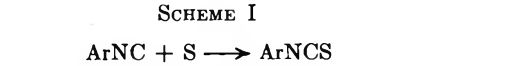


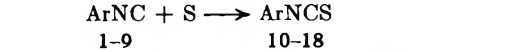


Results

Aryl isocyanides, **1–9** were transformed into isothiocyanates **10–18** by heating each in benzene with sulfur, the preferred reagent, or with phenyl isothiocyanate (Scheme I) (Tables I and II). For three different

SCHEME I





Ar								
$CH_3OC_6H_4$			$O_2NC_6H_4$		$(CH_3O)_2C_6H_3$			C_6H_5 | C_6H_4
o-	*m*-	*p*-	*m*-	*p*-	2,4-	2,5-	3,4-	*o*-
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
10	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**

TABLE I

ISOTHIOCYANATES FROM ISOCYANIDES AND SULFUR[a]

Isocyanides, ArNC			Isothiocyanates, ArNCS		
No.	mmol	Gc rt, min	No.	Yield, %	Gc rt, min
1	1.353	6.2	10	87.3[b]	12.8
2	1.353	4.2	11	44.2	10.8
3	1.353	5.5	12	65.0	14.0
4	1.014	4.2	13	76.2	8.2
5	1.014	4.0	14	79.6	8.5
6	1.000	8.8	15	77.5	16.8
7	1.227	4.2	16	83.6	7.4
8	1.000	1.9	17	82.8	3.2
9	0.894	6.2	18	97.6	10.8

[a] See Experimental Section for gc details; rt, retention time. [b] This value corresponds to 72.5% recovery of 1 and 87.3% yield of 10. A duplicate experiment gave 78.5% recovery of 1 and 84.9% yield of 10.

systems a reversible transfer of sulfur from an isothiocyanate to an isocyanide was demonstrated (Table III).

No interaction between 6 and 12 in benzene at room temperature could be detected after 64 hr and 12 was quantitatively recovered. Under similar conditions sulfur also failed to transform 6 into 15. In refluxing methylene chloride, bp 39°, there was no interaction between 6 and 12 but a trace of 15 was produced after 64 hr from the combination of 6 and sulfur.

(1) Financial support was received from NASA Grant No. NGR 14-012-004.

(2) V. P. Savin, P. V. Naumkin, G. E. Semenova, and S. Ya. Kazakova, *Khim. Prom (Moscow)*, **44**, 550 (1968); *Chem. Abstr.*, **69**, 78824r (1968).

(3) (a) W. Weith, *Chem. Ber.*, **6**, 210 (1873). (b) J. U. Nef, *Justus Liebigs Ann. Chem.*, **280**, 291 (1894). (c) M. Lipp, F. Dallacker, and I. Meier zu Köcker [*Monatsh. Chem.*, **90**, 41 (1959)] reported thermal sulfurization of isocyanides in the presence of amines to produce thioureas. An intermediate isothiocyanate was assumed. In a similar reaction with selenium, an intermediate isoselenocysnate was apparently transformed into a selenourea. (d) Y. Kowaoka [*J. Soc. Chem. Ind., Jap.*, **43**, 151 (1940); *Chem. Abstr.*, **34**, 6487 (1940)] treated phenyl isocyanide with sulfur and carbon disulfide at 151° for 4 hr at pressures up to 200 psi. A solid black mass containing a trace of mercaptobenzothiazole, the only identified product, confirms the earlier report[3a] that trace quantities of phenyl isothiocyanate may be formed from phenyl isocyanide and sulfur.

(4) S. Otsuka and M. Tatsuno, Japanese Patent 70 19,884 (1970); *Chem. Abstr.*, **73**, 98442a (1970).

(5) I. Ugi, "Isonitrile Chemistry," Academic Press, New York, N. Y., 1971, p 66.

(6) (a) H.-W. Wanzlick and B. König, *Chem. Ber.*, **97**, 3513 (1964). (b) N. Latif and I. Fathy [*J. Org. Chem.*, **27**, 1634 (1962)] suggested the intermediate formation of a thiocarbonyl compound by the reaction between a carbene and sulfur in the overall transformation of a diazoalkane and sulfur into a tetrasubstituted ethylene sulfide. (c) D. M. Lemal in "The Chemistry of the Amino Group," S. Patai, Ed., Wiley, New York, N. Y., 1968, pp 701–748.

(7) (a) R. Neidlein, *Angew. Chem.*, **76**, 500 (1964); *Angew. Chem., Int. Ed. Engl.*, **3**, 446 (1964); *Chem. Ber.*, **97**, 3476 (1964); *Arch. Pharm. (Weinheim)*, **298**, 124 (1965). (b) J. Goerdeler and H. Schenk, *Chem. Ber.*, **98**, 3831 (1965); H. Schenk, *ibid.*, **99**, 1258 (1966).

(8) H. E. Winberg and D. D. Coffman, *J. Amer. Chem. Soc.*, **87**, 2776 (1965).

TABLE II

ISOTHIOCYANATES FROM ISOCYANIDES AND PHENYL ISOTHIOCYANATE[a]

Isocyanides, ArNC		Isothiocyanates, ArNCS	
No.	mmol	No.	Yield, %
1	1.000	10	46.1
2	1.128	11	34.0[b]
3	1.209	12	55.7[b-d]
4	1.014	13	52.5
5	1.014	14	26.5[e,f]
6	0.614	15	66.8[b]
7	1.227	16	65.6
8	1.000	17	36.4

[a] See Experimental Section for gc details and Table I for each retention time. Amount of phenyl isothiocyanate was equimolar with **1**, **3**, **4**, **5**, and **8**; in a molar excess of 40% with **2** and 20% with **6**; and in a molar deficiency of 8% with **7**. The presence of phenyl isothiocyanate was detected during the work-up of each reaction mixture by gc and tlc. In the reaction with **6** it was recovered in 62.0% (0.459 mmol). [b] Based on amount isolated from a column chromatographic fraction. Gc analysis was abandoned because of tailing. [c] By ir and tlc *m*-anisidine and its *N*-formyl derivative were detected. [d] Reaction time 90 hr. [e] Determined by a gc comparison of a column chromatographic fraction with authentic data. [f] In a duplicate run a 34% yield of **14** was determined by gc analysis of a concentrated product mixture in chloroform. The higher yield is attributed to further reaction at the gc temperature of 190°.

TABLE III

REVERSIBLE TRANSFER OF SULFUR FROM AN ISOTHIOCYANATE TO AN ISOCYANIDE

$$ArNC + Ar'NCS \rightleftharpoons ArNCS + Ar'NC$$

Mixture composition obtained from an initial equimolar mixture of starting materials, ArNC and Ar'NCS			
ArNC, %[a]	Ar'NCS, %[a]	ArNCS, %[a]	Ar'NC, %[a]
4, 45.0[b]	**12**, 43.2[b]	**13**, 2.2[c]	**3**, trace[d]
3, 29.6[b,e]	**13**, 30.6[f]	**12**, 2.0[f]	**4**, *e*
5, 43.3[b]	**12**, 42.4[b]	**14**, 2.7[c]	**3**, trace[d]
3, 42.1[b]	**14**, 47.2[b]	**12**, 1.1[f]	**5**, none
6, 37.1[f]	**12**, 43.4[f]	**15**, 4.6[f]	**3**, 4.1[f]
3, 44.4[b]	**15**, 44.9[b]	**12**, 3.0[f]	**6**, 1.5[b]
6, 32.8[c]	**12**, 34.9[c]	**15**, 8.1[c]	**3**, 7.2[c]
3, 38.8[c]	**15**, 36.2[c]	**12**, 4.4[c]	**6**, 3.0[c]

[a] Proportion of reaction mixture. Unaccounted for material is assumed to be polymeric. [b] From weight of material isolated by column chromatography. [c] The amount was determined by gc analysis of the concentrated reaction mixture. The differences for mixtures of **6**, **12**, **15**, and **3** are attributed to further reaction at the temperature, 170°, of the gc analysis. [d] Detected by tlc and by odor, identified by comparison with authentic data. [e] The *N*-formyl derivatives of *p*-anisidine and of *m*-nitroaniline were detected by tlc and identified by comparison with authentic values. [f] From gc analysis of a column chromatographic fraction and comparison with authentic data.

p-Methoxyphenyl isothiocyanate (**12**) transformed *m*- and *p*-nitrophenyl and 2,4-dimethoxyphenyl isocyanides (**4**, **5**, and **6**) into the corresponding isothiocyanates **13** and **14** in moderate yields and **15** in higher yield (Table III). Similar reactions with phenyl isothiocyanate (Table II) also revealed higher reactivity in **6** when compared with a nitrophenyl isocyanide (**4** or **5**).

Phenyl isothiocyanate and 2,4-dimethoxyphenyl isothiocyanate (**15**) were each more efficient than a nitrophenyl isothiocyanate (**13** or **14**) in transferring sulfur to *p*-methoxyphenyl isocyanide (**3**).

In very low yield an equimolar mixture of phenyl isocyanide and phenyl isothiocyanate interacted with water on a silica gel column to give thiooxanilide.

Discussion

When heated with sulfur, ethyl and phenyl isocyanides were converted into isothiocyanates; however, no more than a trace amount of unisolated phenyl isothiocyanate was found and a percentage yield of ethyl isothiocyanate was not reported.[3a,b] Without isolation, other isothiocyanates have probably been formed by this reaction; *e.g.*, a thiourea from an isocyanide, sulfur, and an amine probably came from an intermediate isothiocyanate.[3c] Heating phenyl isocyanide, sulfur, and carbon disulfide under pressure gave a solid black mass,[3d] perhaps polymeric.

Identification of a polymer of an aryl isocyanide has not been reported; however, both a bis anil of 4-azanaphthquinone-1,2 which is an orange-red trimer[9] and a bis anil of indigo which is a blue-black tetramer[10] are obtained from phenyl isocyanide. Just as α,α addition, generally initiated by a nucleophilic isocyano carbon, describes many of its other chemical reactions, α,α self-addition, with the formation of only carbon to carbon bonds, would result in the polymerization of an isocyanide.[11] By combining with an isocyano carbon, sulfur could conceivably catalyze polymerization and, at the same time, produce an isothiocyanate.[12] A nucleophilic attack by isocyano carbon upon sulfur is assumed.

$$ArNC \xrightarrow{S_8} \bar{S}S_6\overset{+}{S}C(=NAr) \xrightarrow{ArNC} \bar{S}_8C(=NAr)-\overset{+}{C}(=NAr) \xrightarrow{n\ ArNC}$$

$$\bar{S}_8[C(=NAr)]_m\overset{+}{C}=NAr$$

$$(ArNC)_xS_8 \longrightarrow ArNCS + [(ArNC)_{(x-1)} + S_7]$$

Three dimethoxyphenyl and two nitrophenyl isocyanides are transformed by sulfur into corresponding isothiocyanates in excellent yields, but the results are scattered for the reaction with the three isomeric methoxyphenyl isocyanides (Table I). Inductive substituent effects appear to influence these reactions, as expected in the absence of resonance interaction between the isocyano group and another ring substituent.[13] Possibly an ortho-substituent effect is needed to account for consistently high yields of **10**, **15**, **16**, and **18**. Intramolecular interaction between an *o*-methoxy or an *o*-phenyl substituent and the cationic center in the suggested intermediate adduct could

(9) M. Passerini and T. Bonciana, *Gazz. Chim. Ital.*, **61**, 959 (1931).

(10) C. Grundmann, *Chem. Ber.*, **91**, 1380 (1958).

(11) T. Saegusa, Y. Ito, and S. Kobayashi [*Tetrahedron Lett.*, 521 (1967)] described a polymer of cyclohexyl isocyanide. F. Millich and R. G. Sinclair [*J. Polym. Sci., Part A-1*, **6**, 1417 (1968); *Part C*, **22**, 33 (1968)] reported heterogeneous polymerization of alkyl isocyanides in the presence of a strong acid and a free-radical source. Liquid samples of isocyanides on long storage in amber bottles at room temperature also polymerized. An explanation for a poly-α-phenylethyl isonitrile with repeating imino units was based, in part, on chain propagation by a α,α self-addition to isocyano carbon and detection of the repeating imino group by ir absorption at 1625 cm^{-1} and uv absorption below 220 nm.

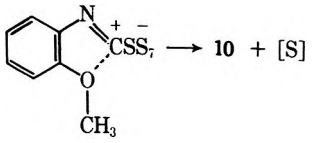
(12) T. G. Levi [*Gazz. Chim. Ital.*, **61**, 619 (1931)] reported polysulfides of aryl isothiocyanates, from which an aryl isothiocyanate may dissociate.

$$C_6H_5NHC(=S)\overset{+}{S}NH_4 + S_2Cl_2 \longrightarrow (C_6H_5NC)_2S_8$$

$$(C_6H_5NC)_2S_8 \xrightarrow[KCN]{C_2H_5OH} C_6H_5NCS + NH_4SCN$$

(13) P. v. R. Schleyer and A. Allerhand, *J. Amer. Chem. Soc.*, **84**, 1322 (1962); **85**, 866 (1963). L. L. Ferstandig, *ibid.*, **84**, 3553 (1962). Reference 5, pp 1–7.

improve the yield of product and decrease the amount of polymer formed. A similar effect might be expected for *o*-nitrophenyl isocyanide, but our efforts to prepare this unknown compound were unsuccessful.



Apart from an interest in the reaction mechanism for the reversible transfer of sulfur from an isothiocyanate to an isocyanide, application to organic synthesis will be limited. There is not only the problem of separating a product from the four-component reaction mixture but also the occurrence of competitive reactions which partially consume both isocyanides and isothiocyanates. These have not been investigated; nevertheless it is assumed that polymerization accounts for a tarry material collected at the top of the chromatographic column in the work-up of each reaction mixture. Trace amounts of formanilides can be attributed to hydration of isocyanides, perhaps by trace amounts of water in the reaction mixture, but more likely by water from the silica column.

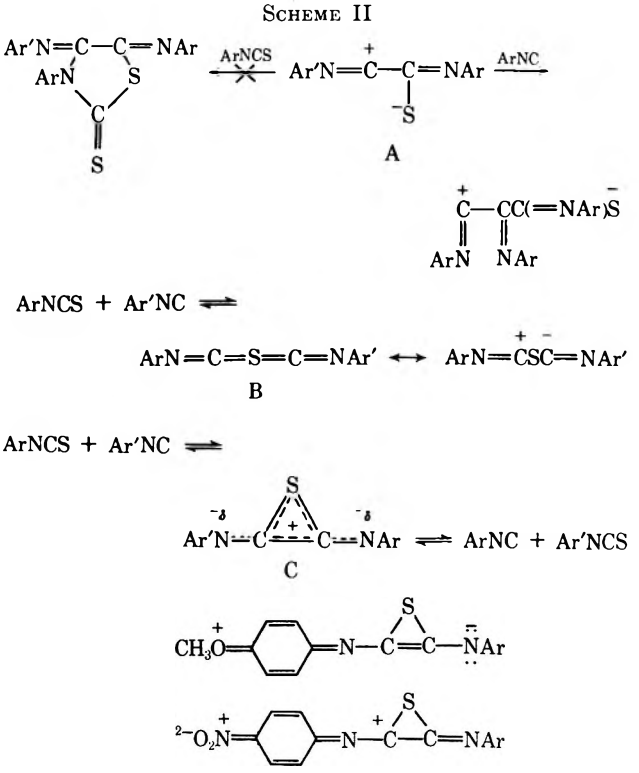
Product separation was fortuitously simplified when phenyl isothiocyanate was the sulfurization reagent. Apparently phenyl isocyanide was rapidly polymerized since no more than trace quantities were detected in any of the reaction mixtures. While this has undoubtedly brought about an increase in the yield of product isothiocyanate, thereby enhancing value in preparative work, sulfur is the reagent of choice for the sulfurization of an isocyanide.

As revealed (Table II) by recovery of starting material, *o*-methoxyphenyl and 2,5-dimethoxyphenyl isocyanides (**1** and **7**) appear to be the least reactive of the isocyanides studied in the presence of phenyl isothiocyanate while *m*-methoxyphenyl and 2,4-dimethoxyphenyl isocyanides (**2** and **6**) appear to be the most reactive. Since unrecovered **1** and **2** are mostly consumed in an unidentified reaction(s), **6** has been judged to be the most efficient of the isocyanides studied in capturing sulfur from phenyl isothiocyanate. *p*-Nitrophenyl isocyanide (**5**) appears to be the least efficient. Similarly **6** is more effective than either *m*- or *p*-nitrophenyl isocyanide (**4** or **5**) in taking sulfur from *p*-methoxyphenyl isothiocyanate (**12**); however, it must also participate more extensively in other reactions to account for total amount consumed (Table III).

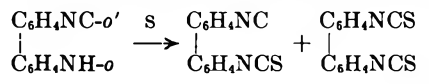
The transfer of sulfur to the isocyanide **3** from the isothiocyanates **13**, **14**, or **15** produced isothiocyanate **12** in yields of 10, 36, and 59%, respectively (Table III). Corresponding limits on competitive but uninvestigated consumption of starting material, including polymerization, were 38, 10, and 6%. Clearly the 2,4-dimethoxyphenyl group makes both the isocyanide **6** and also the isothiocyanate **15** the most productive of each kind for the sulfur transfer, perhaps as a result of inhibiting side reactions. A side reaction which is significant for its absence in all isocyanide–isothiocyanate systems in this study is the dipolar addition of an isothiocyanate to an assumed zwitterionic 1:1 adduct. In contrast the zwitterion $(R_2N)_2C^+$—C(=NC_6H_5)S^- readily combined with an isothiocyanate and other 1,3 dipolariphiles.[8] Of course an isothiocyanate may be a poor competitor with an isocyanide for a dipolariphile such as adduct A.

For the formation of an adduct, a nucleophilic attack by isocyano carbon upon isothiocyanato carbon was expected but has not been differentiated from an attack on sulfur. The latter might give initially a tetracovalent sulfur derivative B.[14] Both A and B are electron-localized forms of adduct C in which lower reactivity may be attributed to resonance. Electron donation, *e.g.*, by an *o*- or *p*-methoxyphenyl group, would tend to stabilize the cationic charge in C. While electron withdrawal, *e.g.*, by an *o*- or *p*-nitrophenyl group, would tend to stabilize the anionic center in C, such resonance interaction would favor an attack by isocyano carbon leading to polymerization (Scheme II).

SCHEME II



An unsuccessful attempt was made to detect an intramolecular "adduct" from 2-isocyano-2′-isothiocyanatobiphenyl which was prepared along with 2,2′-diiso-



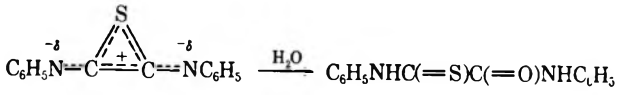
thiocyanatobiphenyl from 2,2′-diisocyanobiphenyl and sulfur. On the other hand a low yield of thiooxanilide was obtained by passing a mixture of phenyl isocyanide and phenyl isothiocyanate over a silica gel column.[15] Addition of water to an intermediate zwitterion C (Ar = Ar′ = C_6H_5) would account for the product. In a similar manner a solid obtained in trace quantity from 2,4-dimethoxyphenyl isocyanide and 2,4-dimethoxyphenyl isothiocyanate may be the corresponding tetramethoxythiooxanilide; however, the tentative identi-

(14) M. Takaku, S. Mitamura, and H. Nozaki [*Tetrahedron Lett.*, 3651 (1969)] generated $(CH_3)_2N)_2C^+SC^-HCO_2CH_3$. M. Carmack, I. W. Stapleton, and R. Y. Yen [*Org. Prep. Proced.*, 1, 255 (1969)] discuss and refer to hetero, tetravalent, sulfur intermediates.

(15) We are indebted to Dr. J. de Jong for first observing this reaction.

fication, supported by the mass spectrum, M^+ 376, and mp 230°, for the yellow solid needs to be confirmed. Further investigation in this area is planned.

$C_6H_5NC + C_6H_5NCS \longrightarrow$



Experimental Section

Instrumental data were obtained from a Barber-Colman Model 5320 flame ionization gas chromatograph with an attached Sargent recorder equipped with an integrator, a Perkin-Elmer Model 237B grating infrared spectrophotometer, a Hitachi-Coleman Model 124 spectrophotometer, a Varian A-60A spectrometer, and a Perkin-Elmer Model 270 gas chromatograph and attached mass spectrometer. Elemental analyses were obtained from Micro-tech Laboratories, Chicago, Ill. For gc analyses the gas chromatograph was equipped with a stainless steel column, 8 ft by 0.25 in., of 5% GE, XE60 on Chromosorb G, 60-80 AW DMGS (Nuclear Chicago); nitrogen was the carrier gas. J. T. Baker silica gel powder, 60–200 mesh, in a column, 12 in. by 1 in., was the adsorbent in column chromatography. Hexane–benzene mixtures, with the ratio progressing from 1:0 to 0:1, eluted the column. Separation by tlc was achieved on strips of ChromAR sheet-500.

Sulfurization of 1 to 2 mmol of each isocyanide **1–9** by either elemental sulfur (1.0 to 1.5 molar excess) or phenyl isothiocyanate was carried out in a solution of 25 ml of anhydrous benzene at reflux temperature for 64 hr. Yields were based on recovered isocyanide and were determined by gc analysis of the concentrated reaction mixture in chloroform. The identity and amount of each component in a reaction mixture were determined by comparison with gc analysis of a standard solution of the authentic material. In addition each component of a reaction mixture was also identified by comparing ir and tlc absorption with authentic data and by mixture melting point wherever possible. Each gc analysis was carried out under a carrier gas pressure of 18–20 psi. The retention times (Table I) were obtained at a column temperature of 132° for **1**, **2**, **3**, **10**, **11**, and **12**; 190° for **4**, **5**, **7**, **13**, **14**, and **16**; 170° for **6** and **15**; 212° for **8** and **17**; and 175° for **9** and **18**. Phenyl isocyanide was occasionally detected by gc analysis of reaction mixtures described in Table II. It was more often detected by odor. Results are found in Tables I and II.

The reaction mixture of four components obtained by the reversible transfer of sulfur from an isothiocyanate to an isocyanide was analyzed for the forward and reverse reaction in three systems. Conditions for the reaction are identical with the ones described above. Reaction mixture composition was determined by gc and column chromatography. Results are found in Table III.

Preparation of Isocyanides. 3,4-Dimethoxyphenyl Isocyanide.—A mixture of 15.3 g (100 mmol) of 3,4-dimethoxyaniline in 125 ml of formic acid (88%) was heated under reflux for 2 hr. After vacuum distillation had removed excess formic acid and the residue had been treated with ice–water, organic material was extracted with chloroform, washed separately with dilute hydrochloric acid, water, aqueous sodium bicarbonate, and water, and dried over magnesium sulfate. Filtration and then removal of solvent left 10.0 g (55%) of 3,4-dimethoxyformanilide as a colorless solid, mp 87–88°, which was recrystallized from a mixture of chloroform and ether.

A solution of 9.0 g (50 mmol) of 3,4-dimethoxyformanilide in 300 ml of methylene chloride and 25 ml of triethylamine in a 500-ml, three-necked, round-bottomed flask equipped with a condenser, a mechanical stirrer, and a condenser cooled by Dry Ice in acetone was cooled in an ice bath and stirred while phosgene gas was introduced through the Dry Ice–acetone cooled condenser until 110 drops were added. Stirring was continued for 1 hr and then ~100 ml of water was added to the reaction mixture. The organic layer was separated, washed with about 200 ml of water, dried over magnesium sulfate, and concentrated by evaporation. The residue was slurried with silica gel and chromatographed by a column, 10 in. by 1.5 in., of silica. Elution with 800 ml of a mixture of benzene–hexane (1:1) removed 6.5 g (79.7%) of 3,4-dimethoxyphenyl isocyanide **8**, mp 48°, as colorless crystals. An analytical sample was obtained by rechromatographing the crude product. Elution with hexane–benzene gave **8** as a colorless crystalline solid: mp 49–50°; ir ($CHCl_3$) 2128 cm^{-1} (NC); nmr ($CDCl_3$) δ 3.84 (s, 6 H, OCH_3), 6.7–7.1 (m, 3 H, aromatic); uv ($CHCl_3$) 254 nm (log ε 4.12), 285 (3.69), 292 (3.67); mass spectrum (70 eV) *m/e* 163 (M^+), 148, 120, 102, 93, 92. *Anal.* Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.35; H, 5.59; N, 8.65. Other isocyanides were known.

Preparation of Isothiocyanates. 2,4-Dimethoxyphenyl Isothiocyanate.—To an ice-cooled solution of 4.1 g (20 mmol) of *N,N'*-dicyclohexylcarbodiimide in 10 ml of carbon disulfide and 4 ml of pyridine a solution of 3.06 g (20 mmol) of 2,4-dimethoxyaniline in 8 ml of pyridine was added dropwise with stirring. After the mixture stirred overnight, ether was added, and a precipitate of dicyclohexylthiourea was removed by filtration. After concentration the filtrate was taken up in chloroform and washed consecutively with water, dilute hydrochloric acid, water, aqueous sodium bicarbonate, and water. After the mixture dried over magnesium sulfate, removal of solvent left a liquid which solidified and was purified chromatographically from a silica gel column. It was eluted immediately by 400 ml of a mixture of benzene–hexane (1:3) and isolated after removal of solvent as 3.05 g (78.2% yield) of a colorless solid: mp 52–53° (after several recrystallizations from hexane an analytical sample, mp 53–53.5°, was obtained); ir ($CHCl_3$) 2128–2041 cm^{-1} (NCS); uv ($CHCl_3$) 274 nm (log ε 4.05), 301 (4.06); nmr ($CDCl_3$) δ 3.83 and 3.90 (2 s, 6 H, OCH_3), 6.3–7.2 (m, 3 H, aromatic); mass spectrum (70 ev) *m/e* 195 (M^+), 180, 163, 152, 137, 120. *Anal.* Calcd for $C_9H_9NO_2S$: C, 55.39; H, 4.65; N, 7.18; S, 16.40. Found: C, 55.24; H, 4.54; N, 7.06; S, 16.48.

The other isothiocyanates were each prepared by the same method or were commercially available. Previously reported[16] as an oil, 3,4-dimethoxyphenyl isothiocyanate was obtained as a colorless solid: mp 48–48.5°; nmr ($CDCl_3$) δ 3.83 (s, 6 H, OCH_3) 6.7–6.8 (m, 3 H, aromatic). *Anal.* Calcd for $C_9H_9NO_2S$: C, 55.39; H, 4.65; N, 7.18; S, 16.40. Found: C, 55.49; H, 4.69; N, 7.07; S, 16.15.

Thiooxanilide was obtained by placing an equimolar mixture of phenyl isocyanide and phenyl isothiocyanate (20.0 mmol each) on a silica gel column. After elution of phenyl isothiocyanate by 500 ml of hexane and then phenyl isocyanide by a mixture of 400 ml of hexane–benzene (3:1), it was eluted from the column by a mixture of 400 ml of hexane–benzene (1:1) and isolated in trace amount as yellow needles, mp and mmp 142–144°,[17] *m/e* 256 (M^+).

A mixture of 204.0 mg (1.0 mmol) of 2,2'-diisocyanobiphenyl[18] and 32.0 mg (1.0 mmol) of sulfur in 25 ml of benzene was heated at reflux for 64 hr. The concentrated product mixture was chromatographed from a silica gel column, 12 in. by 1 in. After sulfur was eluted with 200 ml of hexane, further elution with 300 ml of hexane removed **2,2'-diisothiocyanatobiphenyl** as a colorless semisolid, 18.0 mg, mp 33–36°, 15.4% yield. When the concentrated product mixture was analyzed by gc at a column temperature of 190° the diisothiocyanate, retention time 28.0 min, was found in 14.9% yield, ir ($CHCl_3$) 2128–2041 cm^{-1} (NCS). *Anal.* Calcd for $C_{14}H_8N_2S_2$: C, 62.69; H, 3.01; N, 10.44; S, 23.86. Found: C, 62.59; H, 3.19; N, 10.64; S, 24.09.

Further elution of the column with 600 ml of hexane–benzene (3:1) gave 55.0 mg of **2-isocyano-2'-isothiocyanatobiphenyl** as a light pink semisolid, 53.4% yield. Rechromatographic separation gave an analytical sample as a light pink semisolid. Gc analysis, *vide supra*, gave the product, retention time 19.4 min, in 36.7% yield (presumably some of the isocyanide polymerized at 190°): ir ($CHCl_3$) 2128 (NC), 2128–2041 cm^{-1} (NCS). *Anal.* Calcd for $C_{14}H_8N_2OS$: C, 71.18; H, 3.41; N, 11.86; S, 13.55. Found: C, 71.46; H, 3.63; N, 11.58; S, 13.59.

Further elution of the column with 400 ml of benzene–hexane (1:1) gave unreacted 2,2'-diisocyanobiphenyl, 115.0 mg, retention time 10.0 min, 56.4%, identified by comparison with identical tlc and ir data. Yields are based on the recovered starting material.

(16) G. M. Dyson, H. J. George, and R. F. Hunter, *J. Chem. Soc.*, 436 (1927).

(17) B. Milligan and J. M. Swan, *ibid.*, 2969 (1959).

(18) Unpublished preparation by Dr. J. de Jong.

A repeat sulfurization of 2,2′-diisocyanobiphenyl with a 6 molar excess of sulfur gave 2,2′-diisothiocyanatobiphenyl found in 67.2% yield by isolation from a silica gel column and 87.5% yield by gc (apparently there was additional reaction at 190°). The 2-isocyano-2′-isothiocyanatobiphenyl was found in 10.2% yield by isolation from a silica gel column and was not detected by gc analysis of the product mixture. There was no recovered starting material.

Registry No.—8, 33904-01-7; 3,4-dimethoxyformanilide, 33904-02-8; 2,4-dimethoxyphenyl isothiocyanate, 33904-03-9; 3,4-dimethoxyphenyl isothiocyanate, 33904-04-0; 2,2′-diisothiocyanatobiphenyl, 33904-05-1; 2-isocyano-2′-isothiocyanatobiphenyl, 33904-06-2.

Reactions of Dimethylsulfonium Cyclopentadienylide with Electrophiles and Dienophiles

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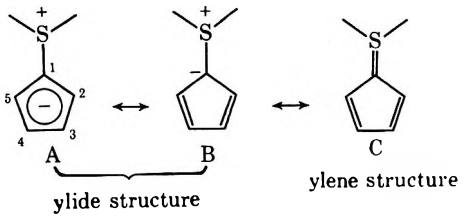
The reactions of dimethylsulfonium cyclopentadienylide (I) with electrophiles and dienophiles have been attempted. Electrophiles such as acetyl chloride, benzenesulfonic acid anhydride, Vilsmeier reagent, and triethyloxonium fluoroborate react with I to give acetyl-, benzenesulfonyl-, diformyl-, and ethyl-substituted derivatives of I, respectively. Dienophiles such as diethyl acetylenedicarboxylate, tetracyanoethylene, and chloranil react with I to afford the respective Michael addition products of I. From these reaction behaviors, an aromatic character of the five-membered ring in I has been discussed.

Dimethylsulfonium cyclopentadienylide (I) is considered to be the resonance hybrid of ylide structures A, B, and ylene structure C. Although I was first synthesized by Behringer[1] in 1965, no reactions of I



have been reported so far except diazo coupling.[1] It was suggested in our previous communication[2] that the ylide structures predominantly contribute to the resonance hybrid of sulfonium and phosphonium cyclopentadienylide on the basis of theoretical consideration of their electronic spectra. In our other communications[3,4] the reaction of triphenylphosphonium cyclopentadienylide (II) with electrophiles and dienophiles were reported and it was found that electrophilic substitutions and Michael additions took place at the 2 position of the five-membered ring in II without cleavage of the C–P bond. In this paper we describe the reactions of I with electrophiles and dienophiles, and discuss which resonance structure (A, B, or C) plays an important role in the reaction.

Results and Discussion

Preparation of I.—Though I was prepared by Behringer, *et al.*,[1] in 1965, their procedure afforded I in only a few per cent yield. We used *N*,*N*-dimethylformamide as a solvent, and kept low temperature during the reaction. This improved procedure afforded I in considerably better yield (15–20%).

Reactions of I with Electrophiles.—The treatment of I with acetyl chloride, benzenesulfonic acid anhydride, Vilsmeier reagent, and triethyloxonium fluoroborate yielded 2-acetyl (III), 2-benzenesulfonyl (IV), 2,5-diformyl (V), and 2-ethyl (VI) derivatives of I, respectively. In the ir spectra of III and V, the carbonyl stretching vibrations were found at 1580 and 1630 cm^{-1} respectively. These shifts to lower wave numbers are attributed to the delocalization of the negative charge of the five-membered ring to the carbonyl oxygen atom. Since the delocalization of the negative charge generally stabilizes the five-membered ring, the derivatives whose substituents have electron-withdrawing nature, such as acetyl, benzenesulfonyl, and formyl, are more stable than I and the ethyl is less stable[5] than I. The position of substitution was determined by the nmr spectrum of each derivative of I. The signal for five-membered ring protons of I appears as an AA′BB′-type multiplet centered at τ 3.8 (4 H) and the exact chemical shifts and the coupling constants were obtained by simulating the spectrum.[6] The part in the lower field of the signal is assigned to the protons at 2,5 positions and the part in the higher field to the protons at 3,4 positions, as similarly in the case of II. The nmr spectrum of III exhibited three multiplets of equal area (1 H) centered at τ 3.0 (doublet of doublets, J = 3,8, 2.3 Hz), 3.5 (doublet of doublets, J = 3.8, 2.3 Hz), and 3.9 (t, J = 3.8 Hz), which are assigned to cyclopentadienyl ring protons. Among these three peaks, one is nearly in the same position as that in I and the other two peaks shift downfield from the cyclopentadienyl ring proton in I. This is well interpreted if the acetyl group is attached to the 2 position[7] of I; *i.e.*, two electron-withdrawing substituents (dimethylsulfonium and acetyl) make two

(1) H. Behringer and F. Scheidl, *Tetrahedron Lett.*, **No. 22**, 1757 (1965).

(2) Z. Yoshida, K. Iwata, and S. Yoneda, *ibid.*, 1519 (1971); K. Iwata, S. Yoneda, and Z. Yoshida, *J. Amer. Chem. Soc.*, **93**, 6745 (1971).

(3) Z. Yoshida, S. Yoneda, H. Hashimoto, and Y. Murata, *Tetrahedron Lett.*, 1523 (1971).

(4) Z. Yoshida, S. Yoneda, Y. Murata, and H. Hashimoto, *ibid.*, 1527 (1971).

(5) VI decomposes within 2 or 3 days under nitrogen atmosphere, whereas I does not decompose for about 1 month even in the air.

(6) Z. Yoshida, S. Yoneda, and M. Hazama, *Chem. Commun.*, 716 (1971).

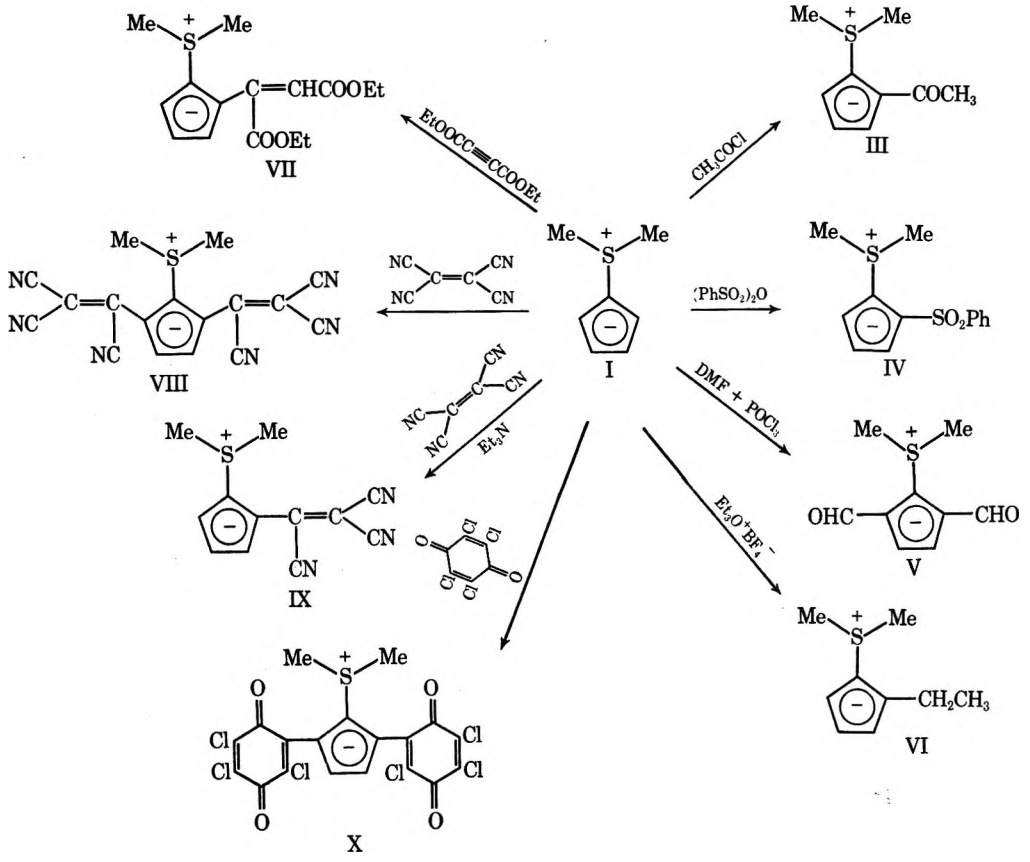
(7) Rationalization of 2 substitution was discussed in the previous publications.[3,8] Lloyd[9] also mentioned the substitution of the 2 position of the cyclopentadienyl ring of II.

(8) Z. Yoshida, S. Yoneda, and Y. Murata, unpublished (to be submitted to *J. Org. Chem.*).

(9) D. Lloyd and M. I. C. Singer, *Chem. Ind.* (*London*), 786 (1971).

SCHEME I

REACTIONS OF I WITH ELECTROPHILES AND DIENOPHILES



protons (3 and 5 positions) shift to lower field. Moreover, the peak (H_4) resonanced in the highest field was split equally by H_3 and H_5 (J = 3.8 Hz) to a triplet, and lower peaks (H_3, H_5) was split with each other (J = 2.3 Hz) and by H_4 (J = 3.8 Hz) to a doublet of doublets. The same tendency was also found in the nmr spectra of IV. This assignment is supported by analogy to the case of phosphonium cyclopentadienylide. The proton signal for the five-membered ring of the *p*-nitrophenylazo derivative of II resembles closely those of III and IV. The substituted position of the *p*-nitrophenylazo derivative of II was experimentally confirmed by Ramirez[10] to be the 2 position.

On the other hand, the signal for the five-membered ring protons of VI exhibited a multiplet centered at τ 3.8 (3 H), in which the intensity diminished by one proton in the part of lower field. This tendency was also found in alkyl derivatives of II.[11] Since the ethyl group scarcely disturbed the electronic state of the five-membered ring, the decrease of the intensity in the lower part indicates that the 2 position was substituted by the ethyl group.

The Reactions of I with Dienophiles.—Upon treatment of I with diethyl acetylenedicarboxylate, the 1:1 adduct (VII) was obtained. The nmr spectrum of VII showed a vinyl proton at τ 4.1 (s, 1 H), five-membered ring protons centered at τ 3.6 (m, 3 H), and signals corresponding to two nonequivalent ethyl groups, methylene protons at τ 5.6 (q, 2 H) and 5.8 (q, 2 H), and methyl protons at τ 8.6 (t, 3 H) and 8.7 (t, 3 H). These nmr data indicate that VII is the Michael addition reaction product as presented in Scheme I. No evidence for Diels–Alder reaction was observed.

When I was treated with tetracyanoethylene in the absence of a base, a 1:2 Michael addition product (VIII) was obtained, while in the presence of thiethylamine only a 1:1 adduct (IX) was obtained. The difference in reaction product in the absence and in the presence of triethylamine is interpreted as follows. When no base was used, before the elimination of hydrogen cyanide from the 1:1 adduct, another molecule of tetracyanoethylene easily added to the 1:1 adduct, followed by elimination of hydrogen cyanide to give the bistricyanovinyl derivative of I. On the other hand, when triethylamine was used as a base, the elimination of hydrogen cyanide immediately would occur before another addition of tetracyanoethylene to the 1:1 adduct. Consequently, the further addition of tetracyanoethylene should be excluded, because a large electron-withdrawing nature of the tricyanovinyl group deactivates the five-membered ring.

The reaction of I with chloranil at 5° gave Michael addition reaction product X, blue crystals. Its nmr spectrum contains a singlet at τ 3.17 (2 H, cyclopentadienyl), clearly indicating that X is the 1:2 adduct of I and chloranil.

Through the reactions of I with dienophiles evidence for Diels–Alder reaction was not obtained, but the products isolated were Michael addition reaction products.

All the reactions of I with electrophiles and dienophiles are summarized in Scheme I. In the comparison of dimethylsulfonium cyclopentadienylide with

(10) F. Ramirez and S. Levy, *J. Amer. Chem. Soc.*, **79**, 6167 (1957).

(11) The alkyl derivatives of II have been recently prepared in our laboratory. The results will be published elsewhere.

triphenylphosphonium cyclopentadienylide, the former is considered likely to be more reactive than the latter, because I reacts with electrophiles and dienophiles under much more mild conditions than II. In summary from the results, it can be concluded that I has an aromatic character; that is, the structure A predominantly contributes to the resonance hybrid of I. The aromatic character of the five-membered ring in I has been also supported by the π-bond orders (P_{23} and P_{34}) estimated from the vicinal coupling constants. The π-bond orders of 0.71 and 0.56 for P_{23} and P_{34} calculated from the $J_{vic} - P_{rs}$ relation proposed by Smith, *et al.*,[12] are clearly within the aromatic range.[6]

Experimental Section

Spectra.—All ultraviolet spectra were taken on a Hitachi EPS-3T recording photometer. All infrared spectra were recorded on a Hitachi grating infrared spectrophotometer, Model 215. All nmr spectra were recorded with a JNM C-60H nmr spectrometer in deuteriochloroform with tetramethylsilane as an internal standard.

Dimethylsulfonium Cyclopentadienylide (I).—To a stirred solution of 100 g (1.5 mol) of cyclopentadiene in 300 ml of *N,N*-dimethylformamide (DMF) was added 240 g (1.5 mol) of bromine at −50 to −30° within 1 hr and the mixture was stirred for an additional 1 hr at this temperature. To the solution, 186 g (3 mol) of dimethyl sulfide in 200 ml of DMF was added below −30°. The orange-yellow colored solution was allowed to stand at 0° for 24 hr. The sulfonium salt precipitated was filtered and poured into 200 ml of water. After decolorization with charcoal, the mixture was made alkaline with 20% aqueous sodium hydroxide and a crude product separated was recrystallized from benzene to give 29 g (15.3%) of colorless needles: mp 134°; uv max (methylene chloride) 283 mμ (ε 1.15 × 10⁴); ir (KBr) 3050, 2980, 2900, 1430 (s), 1420 (s), 1400 (s) 1340, 1320, 1220, 1200 (s), 1190 (s), 1040, 1030, 1020, 980 (s), 710 cm⁻¹ (these infrared absorption bands are characteristic of the derivative of I); nmr ($CDCl_3$) τ 3.8 (m, AA'BB', J_{23} = 3.9, J_{34} = 2.8, J_{24} = 2.1, J_{25} = 1.9 Hz, 4 H, ring), 7.4 (s, 6 H, SCH_3).

Dimethylsulfonium 2-Acetylcyclopentadienylide (III).—To a cooled solution of 1.26 g (0.01 mol) of I dissolved in 50 ml of methylene chloride was added 0.785 g (0.01 mol) of acetyl chloride at −10° under nitrogen atmosphere, and the mixture was stirred for 6 hr at −10°. The reaction mixture was washed with water and dried over calcium chloride, and the solvent was removed under reduced pressure. The residue was chromatographed on alumina and III was obtained as colorless needles (70 mg, 4.2% yield): mp 150°; ir (KBr) 1580 cm⁻¹ ($\nu_{C=O}$); nmr ($CDCl_3$) τ 3.0 (doublet of doublets, J = 3.8, 2.3 Hz, 1 H, ring), 3.5 (doublet of doublets, J = 3.8, 2.3 Hz, 1 H, ring), 3.9 (t, 1 H, ring), 6.95 (s, 6 H, SCH_3), 7.6 (s, 3 H, $COCH_3$).

Anal. Calcd for $C_9H_{12}OS$: C, 64.23; H, 7.14; O, 9.52; S, 19.05. Found: C, 64.49; H, 7.25; O, 9.53; S, 18.92.

Dimethylsulfonium 2-Benzenesulfonylcyclopentadienylide (IV).—To a stirred solution of 1.26 g (0.01 mol) of I dissolved in 50 ml of methylene chloride was added a solution of 3 g (0.01 mol) of benzenesulfonic acid anhydride in methylene chloride at room temperature under nitrogen atmosphere. After stirring for an additional 2 hr, the reaction mixture was neutralized with 5% aqueous sodium hydroxide, extracted with methylene chloride, dried over calcium chloride, and concentrated under reduced pressure. The residual oil was chromatographed on alumina, and 150 mg (5.6%) of IV was obtained as pale yellow needles: mp 164–165°; uv max (acetonitrile) 262 mμ (ε 8.2 × 10³), 292 (1.02 × 10³); ir (KBr) 1340, 1320 (ν_{as} SO_2), 1140 cm⁻¹ (ν_s SO_2); nmr ($CDCl_3$) τ 2.3 (m, 2 H, phenyl), 2.8 (m, 3 H, phenyl), 3.2 (doublet of doublets, J = 3.8, 2.3 Hz, 1 H, ring), 3.5 (doublet of doublets, J = 3.8, 2.3 Hz, 1 H, ring), 3.8 (t, J = 3.8 Hz, 1 H, ring), 7.1 (s, 6 H, SCH_3).

Anal. Calcd for $C_{13}H_{14}S_2O_2$: C, 58.65; H, 5.26; S, 24.06; O, 12.03. Found: C, 58.71; H, 5.84; S, 23.77; O, 11.98.

Dimethylsulfonium 2,5-Diformylcyclopentadienylide (V).—The Vilsmeier reagent was prepared as follows. To 10 ml (0.13 mol) of *N,N*-dimethylformamide was added 1.2 ml (0.024 mol) of phosphorus oxychloride at −10 to −15° under nitrogen atmosphere, and the temperature was elevated to 5°. To this solution, 1.26 g (0.01 mol) of I was added slowly maintaining the temperature at −10 to −15°, and the mixture was stirred for 1 hr at 0°. The reddish precipitate that separated was filtered, shaken with aqueous potassium perchlorate solution, and made alkaline with 50% aqueous sodium hydroxide. The mixture was extracted with methylene chloride and the extract was dried, concentrated, and chromatographed on alumina to give 180 mg (4.4%) of V as pale brown needles: mp 159–160°; uv max (acetonitrile) 263 mμ (ε 1.93 × 10⁴), 326 (6.85 × 10³); ir (KBr) 1630 cm⁻¹ ($\nu_{C=O}$); nmr ($CDCl_3$) τ 0.50 (s, 2 H, CHO), 2.8 (s, 2 H, ring), 6.95 (s, 6 H, SCH_3).

Anal. Calcd for $C_9H_{10}O_2S$: C, 59.31; H, 5.53; S, 17.59. Found: C, 59.49; H, 5.61; S, 17.68.

Dimethylsulfonium 2-Ethylcyclopentadienylide (VI).—To a stirred solution of 1.26 g (0.01 mol) of I in 50 ml of methylene chloride was added 2.0 g (0.0105 mol) of triethyloxonium fluoroborate at 0°, and the mixture was stirred for 1 hr at this temperature. The reaction mixture was then neutralized with 5% aqueous sodium hydroxide and extracted with methylene chloride. The extract was, after removal of the solvent, chromatographed on alumina to give 50 mg of brown precipitate (VI). Elemental analysis of VI was impossible to carry out because of its instability. This material showed ir (KBr) 3080, 3000, 2900, 2880, 2860, 2840 cm⁻¹ (ν_{CH_3}, ν_{CH_2}); nmr ($CDCl_3$) τ 3.80 (m, 3 H, ring), 7.30 (s, 2 H, SCH_3), 7.30 (q, 2 H, J = 7.5 Hz, CH_2), 8.80 (t, 3 H, J = 7.5 Hz, CH_3). These spectral data clearly indicate VI to be the monoethyl derivative of I.

Dimethylsulfonium 2-(1,2-Dicarbethoxyvinyl)cyclopentadienylide (VII).—To a stirred solution of 1.0 g (7.95 mmol) of I in 30 ml of methylene chloride was added 1.45 g (7.95 mmol) of diethyl acetylenedicarboxylate at 5° under nitrogen atmosphere. After stirring for 1 hr at this temperature, the reaction mixture was concentrated under reduced pressure and chromatographed on alumina, and VII was obtained as yellow crystals (2.15 g, 88.7% yield): mp 50°; uv max 390 mμ (ε 1.65 × 10⁴); ir (KBr) 1720, 1680 ($\nu_{C=O}$), 1560 ($\nu_{C=C}$), 1480, and 1140 cm⁻¹; nmr ($CDCl_3$) τ 3.60 (m, 3 H, ring), 4.10 (s, 1 H, vinyl), 5.60 (q, 2 H, J = 7.5 Hz, CH_2), 5.80 (q, 2 H, J = 7.5 Hz, CH_2), 7.27 (s, 6 H, SCH_3), 8.62 (t, 3 H, J = 7.5 Hz, CH_3), 8.70 (t, 3 H, J = 7.5 Hz, CH_3).

Anal. Calcd for $C_{15}H_{20}O_4S$: C, 60.79; H, 6.80; O, 21.59; S, 10.82. Found: C, 60.23; H, 7.08; O, 21.65; S, 10.52.

Dimethylsulfonium 2,5-Bis(tricyanovinyl)cyclopentadienylide (VIII).—To a stirred solution of 1.0 g (7.95 mmol) of I in 50 ml of tetrahydrofuran was added 1.01 g (7.95 mmol) of tetracyanoethylene in tetrahydrofuran at 5° under nitrogen atmosphere. After stirring for 3 hr at this temperature, the reaction mixture was concentrated under reduced pressure and chromatographed on alumina to afford 202 mg (7.8% yield) of red crystals (VIII): mp 220°; uv max (chloroform) 308 mμ (ε 1.07 × 10⁴), 322 (9.85 × 10³), 404 (3.12 × 10⁴), and 524 (6.00 × 10⁴); ir (KBr) 2200 (ν_{CO}), 1500 ($\nu_{C=C}$), 1300 cm⁻¹; nmr (DMSO-d_6) τ 2.20 (m, 2 H, ring), 6.70 (s, 6 H, SCH_3).

Anal. Calcd for $C_{17}H_8N_6S$: C, 62.18; H, 2.46; N, 25.59; S, 9.76. Found: C, 61.95; H, 2.53; N, 25.42; S, 970.

Dimethylsulfonium 2-Tricyanovinylcyclopentadienylide (IX).—To a stirred solution of 1.0 g (7.95 mmol) of I and 8.1 g (7.95 mmol) of triethylamine in 50 ml of tetrahydrofuran was added 1.01 g (7.95 mmol) of tetracyanoethylene in tetrahydrofuran at 5° under nitrogen atmosphere, and the mixture was allowed to stir at this temperature for 3 hr. The reaction mixture was concentrated under reduced pressure and chromatographed on alumina to yield 240 mg (13.3%) of orange crystals (IX): mp 205°; uv max (chloroform) 260 mμ (ε 2.18 × 10³), 428 (2.07 × 10⁴), and 458 (2.79 × 10⁴); ir (KBr), 2200 (ν_{CN}), 1530 ($\nu_{C=C}$), 1380, 950 cm⁻¹; nmr (DMSO-d_6) τ 3.10 (m, 3 H, ring), 6.90 (s, 6 H, SCH_3).

Anal. Calcd for $C_{12}H_9N_3S$: C, 63.43; H, 3.99; N, 18.49; S, 14.11. Found: C, 63.33; H, 4.00; N, 18.79; S, 14.20.

Preparation of X.—To a stirred solution of 1.0 g (7.95 mmol) of I in 50 ml of methylene chloride was added 1.95 g (7.95 mmol) of chloranil at 5° under nitrogen atmosphere. After stirring at this temperature for 2 hr, the reaction mixture was concentrated under reduced pressure and chromatographed on alumina to give 145 mg (8.1% yield) of blue crystals: mp 330° dec; uv max

(12) W. B. Smith, W. H. Watson, and S. Chiranjeevi, *J. Amer. Chem. Soc.*, **89**, 1438 (1967).

(chloroform) 281 mμ (ε 4.10 × 10⁴), 630 (6.20 × 10³); ir (KBr) 1680, 1650 ($\nu_{C=O}$), 1530 ($\nu_{C=C}$), 1110 cm⁻¹; nmr ($CDCl_3$) τ 3.17 (s, 2 H, ring), 7.00 (s, 6 H, SCH_3).

Anal. Calcd for $C_{19}H_8O_4SCl_6$: C, 41.87; H, 1.48; O, 11.74. Found: C, 42.87; H, 1.61; O, 11.23.

Registry No.—I-B, 29164-15-6; I-C, 25158-32-1; III, 33834-93-4; IV, 33830-74-9; V, 33830-75-0; VI, 33830-76-1; VII, 33830-77-2; VIII, 33830-78-3; IX, 33830-79-4; X, 33830-80-7.

Acknowledgment.—We wish to thank Messrs. T. Yato and Y. Kumada for their technical assistance.

The 1,3,2-Dioxaphospholene–Sulfenyl Chloride Condensation. Scope and Mechanism

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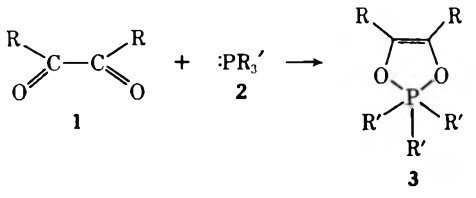
Sulfenyl chlorides condense exothermically with 1,3,2-dioxaphospholenes to form α-chloro-β-keto sulfides in high yield. The exact nature and number of products depend on the structure of the 1,3,2-dioxaphosphophospholene. Several mechanisms were considered and the "sulfenium chloride" pathway is favored.

Trivalent phosphorus compounds are known to react with α-dicarbonyl derivatives to form 1:1 adducts which have been shown to be substituted 1,3,2-dioxaphospholenes **3**.[2,3] These adducts undergo a wide



1 + :PR_3' **2** → **3**

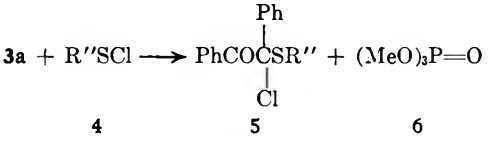
	R		R′		R	R′
1a	C_6H_5	**2a**	CH_3O	**3a**	CH_3O	C_6H_5
1b	CH_3	**2b**	$(CH_3)_2N$	**3b**	$(CH_3)_2N$	C_6H_5
				3c	CH_3O	CH_3
				3d	$(CH_3)_2N$	CH_3

variety of reactions which are of both synthetic and mechanistic interest. For example, the reactivity of 1:1 dicarbonyl–phosphine adducts toward electrophilic centers is attested by their ready condensation with bromine,[4a] carbonyl compounds,[4b] acid chlorides,[4c] isocyanates,[4d] and ketene.[4e] We wish to report that the 1:1 dicarbonyl–phosphine adducts condense exothermically with a variety of sulfenyl chlorides.[5] The nature and the number of final products depend on the type of 1:1 adduct used. This paper describes the scope and mechanism of the condensation.

Results and Discussion

In this investigation, benzil (**1a**) and biacetyl (**1b**) were allowed to react with trivalent phosphorus compounds trimethyl phosphite (**2a**) and tris(dimethylamino)phosphine (**2b**). Of the four possible 1:1 adducts, **3a–c** were prepared according to reported procedures.[6,2d] In our hands, the preparation of the 1:1 biacetyl–tris(dimethylamino)phosphine adduct (**3d**, R′ = Me, R = NMe_2) was not successful; only a black tarry product was obtained.

Adduct **3a** reacted with a variety of sulfenyl chlorides **4** to give α-chloro-β-keto sulfides **5** and trimethyl phosphate **6** according to the following equation.[7]



3a + R″SCl → PhCOCSR″ + $(MeO)_3P{=}O$ (Ph, Cl)

4 **5** **6**

The yields and relevant data of the α-chloro-β-keto sulfides **5** are summarized in Table I.

The progress of this condensation was monitored by nmr. As the addition of sulfenyl chloride progressed, the doublet at τ 6.35 (J = 13 Hz; OCH_3 of **3a**) diminished in intensity as the doublet at τ 6.30 increasingly appeared. Once the addition of sulfenyl chloride was over, the doublet at τ 6.35 had disappeared completely. Trimethyl phosphate was identified by gas chromatography (glpc). The formation of the products appears to be quantitative, although isolated yields are somewhat lower.

The infrared spectra of the α-chloro-β-keto sulfides **5** all show a carbonyl band at 1685 cm⁻¹. The methylene protons α to sulfur in **5d**, **5e**, and **5f** are observed to be diastereotopic[8] even though they are separated from the asymmetric center by a sulfur atom. The methylene protons of **5e** (R″ = CH_3CH_2) were a complex multiplet, thus indicating ABX_3 rather than A_2X_3 splitting. In the case of **5d** (R″ = $PhCH_2$) and **5f** (R″ = CH_2CO_2Me), AB quartets with coupling constants 12 and 16 Hz, respectively, were observed. These values indicate that the AB quartet was derived from vicinal coupling.[9]

(1) Holder of National Research Council of Canada Scholarship, 1967–1970.

(2) (a) L. D. Quinn, G. Pfundt, and G. O. Schenk, in "1,4 Cycloaddition Reactions," J. Hamer, Ed., Academic Press, New York, N. Y., 1967, pp 83–96, 379–388. (b) F. Ramirez, *Pure Appl. Chem.*, **9**, 337 (1964), *Bull. Soc. Chim. Fr.*, 2443 (1966), *Accounts Chem. Res.*, **1**, 168 (1968). (c) F. Ramirez, S. L. Glaser, A. J. Bigler, and J. F. Pilot, *J. Amer. Chem. Soc.*, **91**, 496 (1969). (d) F. Ramirez, A. V. Patwardhan, H. J. Kugler, and C. P. Smith, *Tetrahedron Lett.*, 3053 (1966). (e) Some adducts of $(Me_2N)_3P$ with diketones exist in the phosphonium enolate form.[2d]

(3) Throughout this paper substituted 1,3,2-dioxaphospholenes will be referred to as 1:1 dicarbonylphosphine adducts.

(4) (a) F. Ramirez and N. B. Desai, *J. Amer. Chem. Soc.*, **82**, 2652 (1960); (b) F. Ramirez, A. V. Patwardhan, and C. P. Smith, *J. Org. Chem.*, **31**, 3159 (1966); (c) F. Ramirez, S. B. Bhatia, A. J. Bigler, and C. P. Smith, *ibid.*, **33**, 1192 (1968); (d) F. Ramirez, S. B. Bhatia, and C. P. Smith, *J. Amer. Chem. Soc.*, **89**, 3030 (1967); (e) *ibid.*, **89**, 3026 (1967).

(5) A preliminary account of this work has been published: D. N. Harpp and P. Mathiaparanam, *Tetrahedron Lett.*, 2089 (1970).

(6) F. Ramirez and N. B. Desai, *J. Amer. Chem. Soc.*, **85**, 3252 (1963).

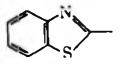
(7) Adducts such as **3a** were prepared *in situ* and dissolved in a suitable solvent (carbon tetrachloride, benzene, or methylene chloride). The color change (discharging of the red sulfenyl chloride) during the addition of sulfenyl chloride was used to follow all the reactions studied.

(8) K. Mislow in "Introduction to Stereochemistry," W. A. Benjamin, New York, N. Y., 1966, pp 93–95; M. Raban and F. B. Jones, Jr., *J. Amer. Chem. Soc.*, **93**, 2692 (1971).

(9) R. M. Silverstein and G. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1967, p 144.

TABLE I

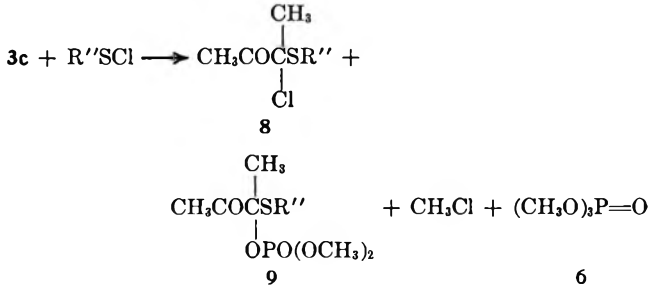
PHYSICAL, ANALYTICAL, AND SPECTROSCOPIC DATA OF α-BENZOYL-α-CHLOROBENZYL SULFIDES 5

R'' in 5	Mp of 5, °C	Yield, %	Calculated, % C	H	S	Cl	Found, % C	H	S	Cl	Nmr data, τ
p-$CH_3C_6H_4$ (5a)	118–120	80	71.47	4.86	9.09	10.05	71.32	4.86	9.04	9.82	2.10–3.20 (14 H, m); 7.72 (3 H, s)
C_6H_5 (5b)	113–115	82	70.88	4.46	9.46	10.46	70.94	4.52	9.35	10.02	2.10–3.00 (m)
p-ClC_6H_4 (5c)	122–124	83	54.34	3.78	8.59	18.99	64.31	3.86	8.57	19.04	2.10–3.00 (m)
$C_6H_5CH_2$ (5d)	109–110	80	79.21[a]	5.70	7.55		79.19	5.76	7.53		2.00–3.00 (15 H, m); 6.15 (2 H, AB, J = 12 Hz)
CH_3CH_2 (5e)	Oil	60	76.12[a]	6.12	8.85		76.06	6.12	8.90		1.80–3.10 (10 H, m); 7.30–7.90 (2 H, m); 8.60–9.20 (3 H, m)
$CH_3O_2CCH_2$ (5f)	65–67	75	70.91[a]	5.46	7.88		70.76	5.57	7.86		1.90–2.65 (10 H, m); 6.34 (3 H, s), 6.53 (2 H, AB, J = 16 Hz)
 (5g)	135–136	93	63.70	3.56	16.20	8.96	63.36	3.56	16.31	9.57	1.80–2.90 (m)

[a] Analyses were performed on the corresponding benzyloxyketo sulfides.

The condensation of adduct **3b** with sulfenyl chlorides proceeds in an analogous manner to the previous reaction. For example, with *p*-toluenesulfenyl chloride **4a** (R'' = *p*-tolyl), gas chromatographic analysis of the mixture indicated the presence of hexamethylphosphoramide **7** and the α-chloro-β-keto sulfide **5a**. In addition, **5a** was isolated from the reaction mixture and was shown to be identical with an authentic sample (prepared from **3a** and **4a**).

Adduct **3c** condensed with sulfenyl chlorides to give α-chloro-β-keto sulfide **8**, trimethyl phosphate **6**, the β-keto phosphate **9**, and methyl chloride according to the following equation.



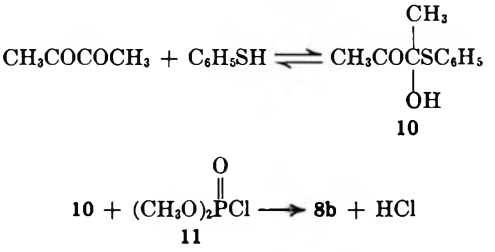
Benzene- and ethanesulfenyl chlorides were used in carbon tetrachloride as solvent. The reaction mixture was analyzed by nmr. When benzenesulfenyl chloride was used, 93% of keto sulfide **8a** was realized along with 7% of the β-keto phosphate **9a**. The ratio of products was altered somewhat in the reaction with ethanesulfenyl chloride (**8b**, 72%; **9b**, 28%).

The nmr spectra of the reaction of adduct **3c** with benzene- and ethanesulfenyl chlorides are illustrated in Figures 1 and 2. In both cases, the singlet at τ 7.00 was identified as arising from methyl chloride.[10] On evaporation of the solvent at room temperature this singlet disappeared. The doublet at τ 6.30 (J_{P-H} = 12 Hz) was due to trimethyl phosphate by comparison with an authentic sample. Also, addition of few drops of trimethyl phosphate to the reaction mixture increased the intensity of this doublet with respect to other peaks.

Considering the reaction between benzenesulfenyl chloride and adduct **3c** (*e.g.*, Figure 1) in detail, the singlets at τ 8.32 and 7.63 can be attributed to the CH_3 and CH_3CO protons of the α-chloro-β-keto sulfide **8a** by comparison with an authentic sample.[11] The singlets at τ 7.80 and 7.67 and the doublet at τ 6.22 (J_{P-H} = 12 Hz) were assigned to the CH_3, CH_3CO, and OCH_3 protons of β-keto phosphate **8b**. All attempts toward the unequivocal synthesis of **8b** were unsuccessful. Synthetic Schemes I and II were tried.

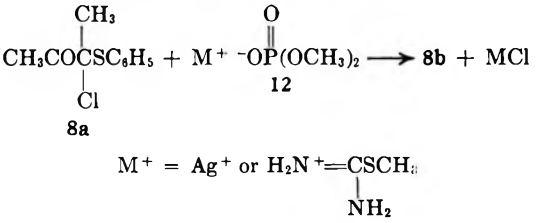
SCHEME I

ATTEMPTED SYNTHESIS OF β-KETO PHOSPHATE 8b



SCHEME II

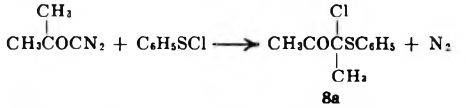
ATTEMPTED SYNTHESIS OF β-KETO PHOSPHATE 8b



In Scheme I biacetyl reacted exothermically with benzenethiol to form an equilibrium mixture containing 80% of the α-hydroxy-β-keto sulfide **10** (analyzed by nmr).[12] When dimethyl phosphorochloridate **11** was added to this mixture at room temperature, no reaction was observed after 2 days. On heating,

(10) One reported value is τ 6.95, ref 9, p 144.

(11) Prepared from azibutanone (diazobutanone) and benzenesulfenyl chloride; see Experimental Section for details.



(12) It has been shown that thiols react with carbonyl compounds to form an equilibrium mixture containing mainly α-hydroxy sulfides; *cf.* E. Campaigne in "Organo-Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, Elmsford, N. Y. 1961, Chapter 14. In the above synthetic scheme the reaction was extended to α diketones.

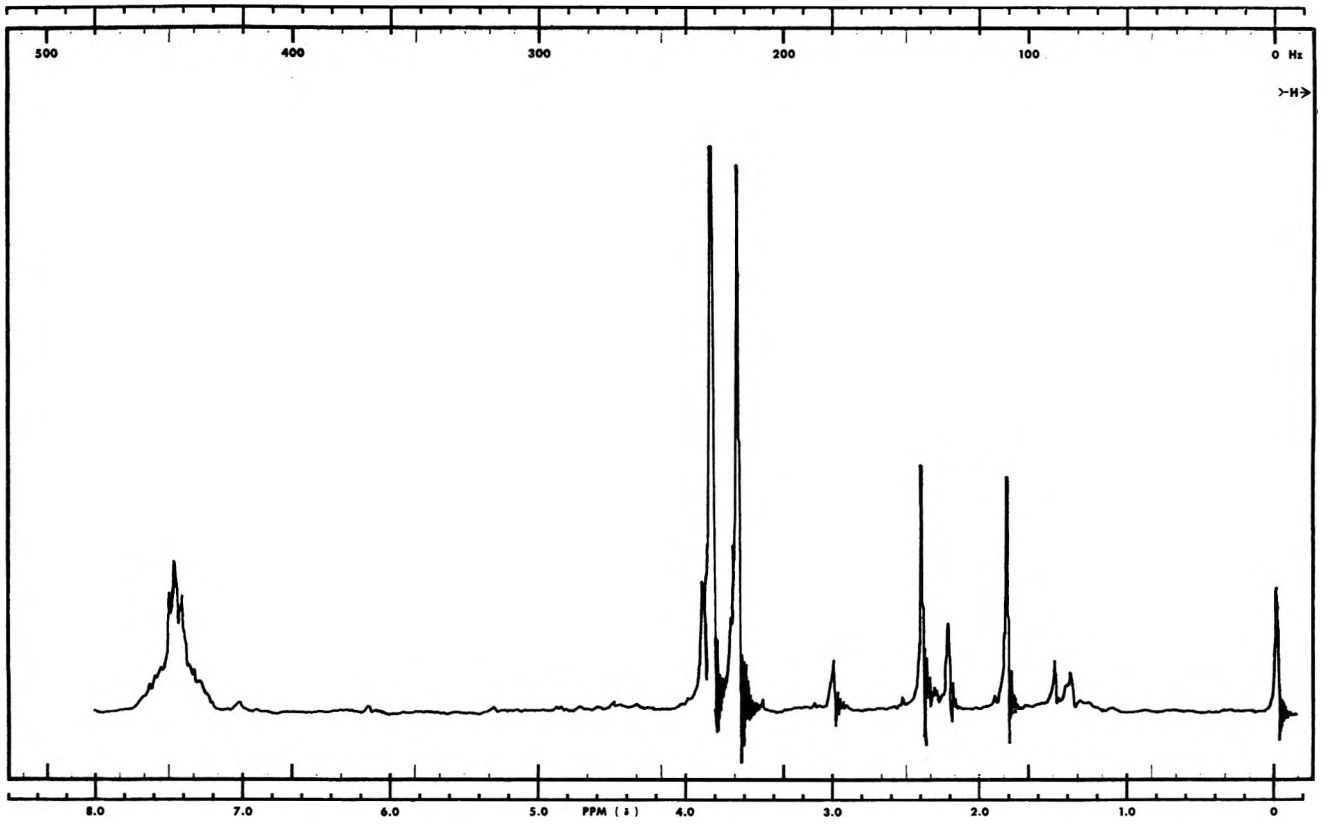


Figure 1.—Reaction of benzenesulfenyl chloride with **3c**.

extensive decomposition occurred. In another attempt, the same procedure was repeated in the presence of pyridine as hydrogen chloride scavenger. The analysis of the reaction mixture by nmr indicated the presence of biacetyl as the main product.

In Scheme II the nucleophilic displacement of the chlorine atom of **8a** with the dimethyl phosphate anion **12** was attempted in acetonitrile. The anticipated β-keto phosphate **8b** was not obtained; only a complex mixture of intractable decomposition products resulted.

Owing to the low stability of the products from the sulfenyl chloride condensation, separation of the β-keto phosphate **8b** either by fractional distillation or by preparative glpc was not achieved. However, the mass spectrum of the reaction mixture revealed the molecular ion of **8b** at *m/e* 304 and two other ions of medium intensity at *m/e* 126 and 127. While the intensity of the molecular ion at *m/e* 304 was too weak for exact mass measurement, the exact masses were determined for ions at *m/e* 126 and 127. Details of these experiments are summarized in Table II. These

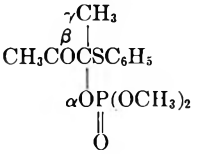
TABLE II

MASS SPECTRAL DATA ON IONS *m/e* 126 AND 127

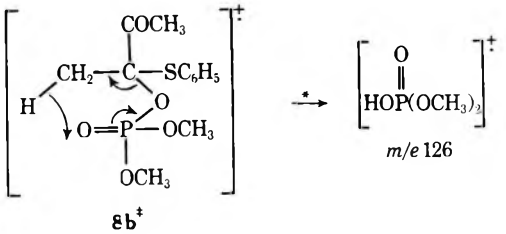
Exact mass		Chemical	
Calcd	Found	formula	Possible structure
126.0082	126.0083	$C_2H_7O_4P$	$(CH_3O)_2P(O)OH$
127.0160	127.0164	$C_2H_8O_4P$	$(CH_3O)_2P(OH)_2$

ions were not present in the mass spectra of pure samples of α-chloro-β-keto sulfide **8a** and trimethyl phosphate. Thus, they appeared to be derived from the β-keto phosphate **8b**.

The mass spectra of several organic phosphates have been studied in some detail.[13] A distinct difference in fragmentation patterns was observed between phosphates with and without γ hydrogens to phosphorus.[14] The essential difference between trimethyl phosphate and the β-keto phosphate **8b** is that the latter has three γ hydrogens. Therefore, it is reasonable to suggest



that these γ hydrogens are involved in the formation of ions at *m/e* 126 and 127 in **8b**. Fragment *m/e* 126 is probably formed by a McLafferty rearrangement of molecular ion $\mathbf{8b}^{\pm}$ as shown. The formation of ion *m/e* 127 could be rationalized as follows. Ion $\mathbf{8b}^{\pm\pm}$, formed by α-carbonyl cleavage, probably undergoes two



$\mathbf{8b}^{\pm}$

(13) H. Budzikiewicz, C. Djerassi, and D. H. Williams in "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, pp 647–653.

(14) For example, the presence of ions at *m/e* 126 and 127 in triethyl phosphate and their absence in trimethyl phosphate could be attributed to the availability of γ hydrogens in the former.

$(\overset{\gamma}{C}H_3\overset{\beta}{C}H_2\overset{\alpha}{O})_3P{=}O$ $(\overset{\beta}{C}H_3\overset{\alpha}{O})_3P{=}O$

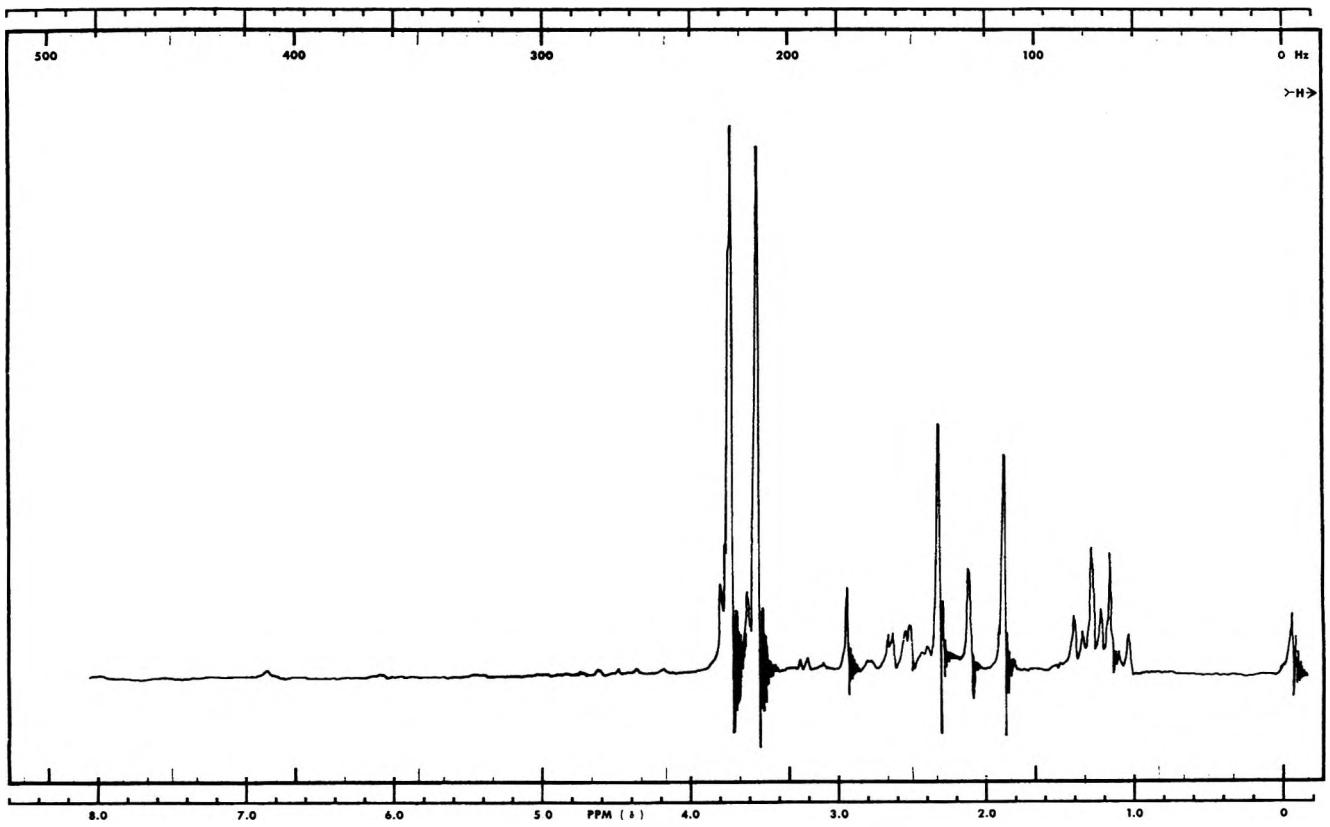
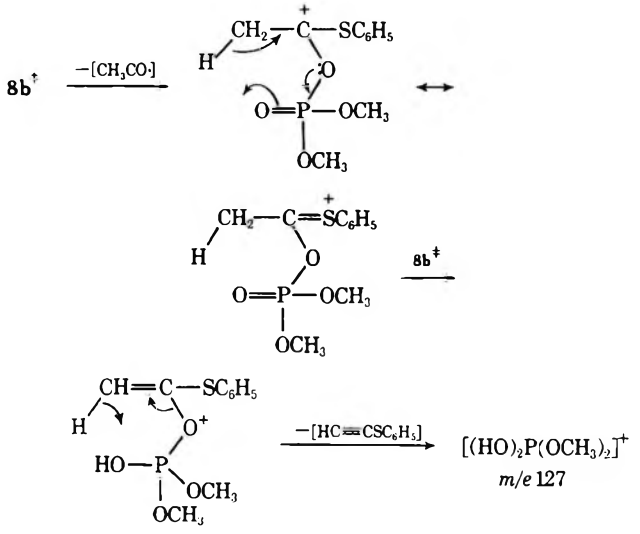
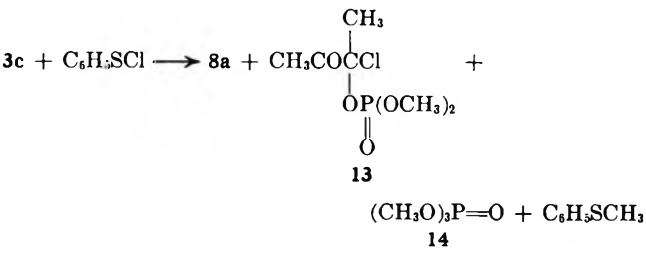


Figure 2.—Reaction of ethanesulfenyl chloride with **3c**.



hydrogen shifts with the elimination of phenylthioacetylene to form ion *m/e* 127.

On mechanistic grounds (*vide infra*), products **13** and **14** could also be expected from the sulfenyl chloride



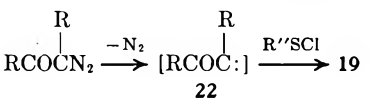
condensation. The nmr signals associated with trimethyl phosphate and α-chloro-β-keto sulfide **8a** were identified. The absence of products **13** and **14** was conclusively demonstrated by comparing the nmr spectrum of the reaction mixture with those of the authentic samples of **13** and **14**. The singlet at τ 7.73 due to the methyl protons of **14** did not correspond with any of the peaks in the nmr spectrum of the reaction mixture. Furthermore, addition of a few drops of **14** to the reaction mixture produced a new singlet at τ 7.73. Authentic α-chloro-β-keto phosphate **13** was prepared according to a reported procedure[15] by the action of chlorine on **3c**. Again, the singlets associated with the CH_3 (τ 7.93) and CH_3CO (τ 7.59) of **13** did not correspond with those of the reaction mixture. This was further checked by addition of **13** to the reaction mixture.

Mechanism.—Several mechanisms can be advanced for this condensation based on the chemistry of both 1:1 dicarbonyl–phosphine adducts and sulfenyl chlorides. A free-radical pathway has been proposed for the reaction of the adduct **3c** with bromotrichloromethane.[16] By analogy, a similar mechanism can be advanced for the sulfenyl chloride condensation. The reaction of adduct **3a** with *p*-toluenesulfenyl chloride (**4a**) was used to test this possibility. The condensation proceeded in the dark and in the presence of a free-radical inhibitor (1,3,5-trinitrobenzene) with no appreciable change in the rate. Furthermore, gas chromatographic analysis of the reaction mixture revealed the absence of *p*-tolyl disulfide, indicating the formation of the *p*-tolylthiyl (*p*-$CH_3C_6H_4S\cdot$) radical is not important. In other free-radical reactions involving thiyl radicals, disulfides are often formed as byproducts.[17] These observations make the free-radical chain mechanism unlikely.

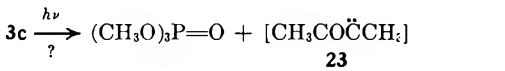
A carbene mechanism has been suggested for the for-

(15) F. Ramirez and N. B. Desai, *J. Amer. Chem. Soc.*, **82**, 2652 (1960).
(16) W. G. Bentrude, *ibid.*, **87**, 4026 (1965).
(17) N. Kharasch and Z. S. Ariyan, *Chem. Ind.* (*London*), 929 (1964).

mation of α-chloro-β-keto sulfides **19** by the action of sulfenyl chlorides on α-diazo ketones **21**.[18] Also, adduct **3c**, when irradiated in cyclohexane, gave tri-



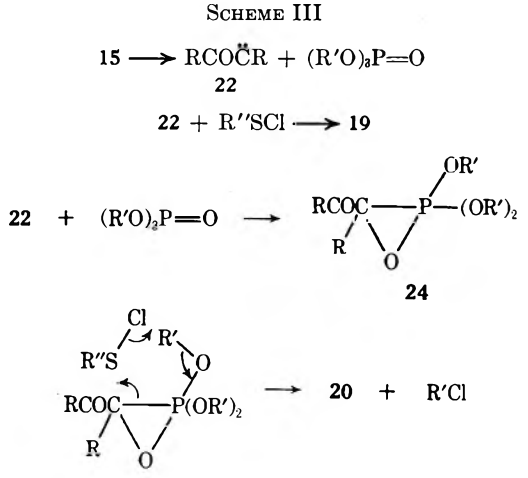
methyl phosphate, trimethyl phosphite, and biacetyl as products.[19] The formation of trimethyl phosphate indicates that a ketocarbene **23** might have been gener-



ated on photolysis.[20] Furthermore, mechanisms involving a carbene by elimination of phosphate[21] or thiophosphate[22] have been suggested for several reactions.

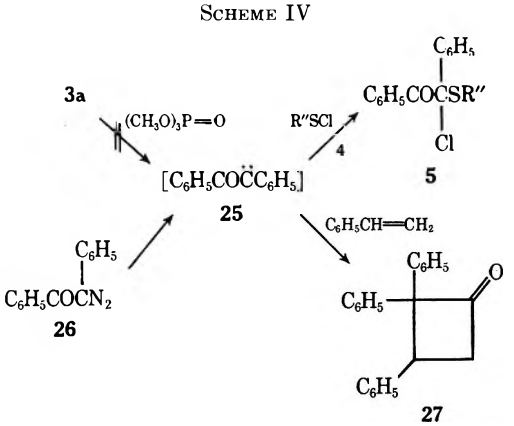
From these studies, it is therefore reasonable to propose a carbene mechanism (Scheme III) for the

SCHEME III



sulfenyl chloride condensation. Several experiments (Scheme IV) were designed to test the validity of this

SCHEME IV

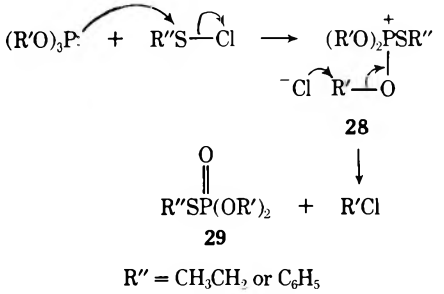


mechanism. Benzoylphenylcarbene (**25**) obtained from benzoylphenyldiazomethane (**26**) reacting with *p*-toluenesulfenyl chloride (**4a**, R″ = *p*-tolyl) to give the α-chloro-β-keto sulfide **5a** in good yield. Also, keto-

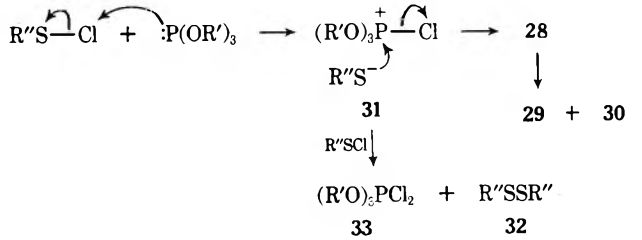
(18) F. Weygand and H. J. Bestmann, *Z. Naturforsch. B*, **10**, 296 (1955).
(19) W. G. Bentrude, *Chem. Commun.*, 174 (1967).
(20) The mechanistic details of this reaction have not yet been reported.
(21) F. Ramirez, H. Yamanaka, and O. H. Basedow, *J. Amer. Chem. Soc.*, **83**, 173 (1961).
(22) E. J. Corey and R. A. E. Winter, *ibid.*, **85**, 2677 (1963).

carbene **25** has been shown to be intercepted by styrene to give cyclobutanone **27**.[23] However, under identical conditions, adduct **3a** did not give **27** when treated with styrene. Thus, the possibility of a carbene mechanism seems remote for the sulfenyl chloride condensation.

Any ionic mechanism for the sulfenyl chloride condensation should take into account the two possible modes of polarization of sulfenyl chlorides, namely, a "sulfenium chloride" mode ($R''S^{\delta+}Cl^{\delta-}$) and a "chloronium mercaptide" mode ($R''S^{\delta-}Cl^{\delta+}$). Even though the former polarization has been favored in most of the reactions of sulfenyl chlorides,[24] the latter has been shown to occur in some reactions (*e.g.*, involving *p*-nitrobenzenesulfenyl chloride). The reactions of ethane- and benzenesulfenyl chlorides with trialkyl phosphites[25] illustrate the sulfenium chloride polarization. The phosphite attacks the electrophilic sulfur to form the phosphonium intermediate **28**. The chloride



ion is sufficiently nucleophilic to dealkylate the phosphonium intermediate **28** by preferential attack on an alkoxy carbon to form the energetically favored P=O bond. An alternative chloronium mercaptide mechanism would involve an initial attack of the phosphite on the chlorine similar to that observed in *tert*-butyl hypochlorite.[26] In this case, attack on chlorine seems less likely, because the mercaptide ion ($R''S^-$) would itself be strongly thiophilic and would be expected to react rapidly with remaining sulfenyl chloride to form disulfide **32** and the dichlorophosphorus compound **33**.

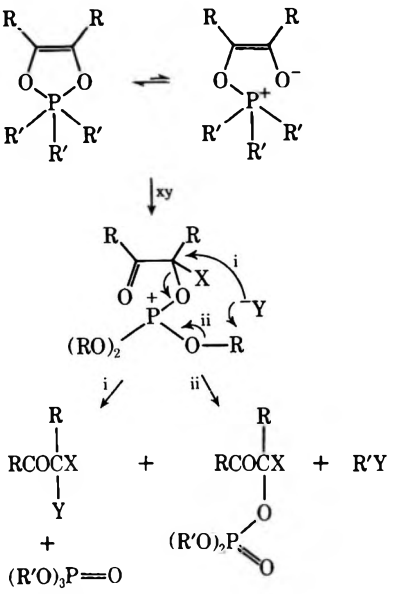


This chloronium mercaptide polarization of sulfenyl chlorides has been observed in the reaction of *p*-nitrobenzenesulfenyl chloride (R″ = p-$NO_2C_6H_4$) with triphenyl phosphite (R = Ph).[27] Based on these analogies, in the condensation of benzenesulfenyl chloride **4b** with the adduct **3c**, the following set of products would be expected by the two proposed

(23) C. S. Marvel and M. I. Kohan, *J. Org. Chem.*, **16**, 741 (1951). In this case, the ketocarbene **5** rearranged to diphenylketene ($Ph_2C{=}C{=}O$) before addition to styrene. The assignment of structure **27** for the cyclobutanone was confirmed by ir and nmr spectra (see Experimental Section.)
(24) W. H. Mueller, *Angew. Chem., Int. Ed. Engl.*, **8**, 482 (1969), and references cited therein.
(25) D. C. Morrison, *J. Amer. Chem. Soc.*, **77**, 181 (1955).
(26) D. B. Denney and R. R. DiLeone, *ibid.*, **84**, 4737 (1962).
(27) K. A. Petrov, G. A. Sokolskii, and B. M. Poleers, *Zh. Obshch. Khim.*, **26**, 2281 (1956); *Chem. Abstr.*, **51**, 9473 (1957). (b) *p*-Nitrophenyl disulfide and triphenoxyphosphorus dichloride were isolated in good yields.

SCHEME V

IONIC MECHANISMS



sulfenium chloride mechanism: X = SR''; Y = Cl

chloronium mercaptide mechanism: X = Cl; Y = SR''

mechanisms (Scheme V). It has been shown earlier that the products formed in the condensation correspond to those predicted by the sulfenium chloride mechanism. Thus, it appears that the condensation in this case proceeds *via* the above mechanism. The absence of phenyl disulfide in the reaction mixture (checked by glpc) makes the chloronium mercaptide mechanism unlikely.

In the 1:1 benzil–trimethyl phosphite adduct (**3a**)–sulfenyl chloride condensation, the only products observed are the α-chloro-β-keto sulfide **5** and trimethyl phosphate. Although, these products can be accounted by both mechanisms, the sulfenium chloride pathway is preferred because there is no disulfide formation. It seems that in this case, path i is followed exclusively to path ii. This could be rationalized as follows. In path i, the tertiary carbon undergoing nucleophilic attack is not only benzylic but also α to the carbonyl group and to sulfur. All these characteristics accelerate the substitution at the carbon.[28] Moreover, additional driving force is introduced into path i by the elimination of the very stable trimethyl phosphate through energetically favored P=O bond formation. In path ii even though there are three primary carbons which can undergo nucleophilic attack, the only driving force available is P=O bond formation. In the 1:1 biacetyl–trimethyl phosphite adduct (**3c**)–sulfenyl chloride condensation (R = R' = Me), which lacks the benzylic group, path ii competes with path i to a significant extent.

The condensation of sulfenyl chlorides with 1:1 benzil–tris(dimethylamino)phosphine adduct **3b** can also be rationalized on the basis of sulfenium chloride mechanism. This condensation is similar to that of the adduct **3a** with sulfenyl chlorides, except that path ii is not important.

(28) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, pp 280–289.

Experimental Section

Melting points were obtained on a Gallenkamp melting point apparatus and are corrected. Infared spectra were recorded on a Perkin–Elmer (Model 257 or 337) grating infrared spectrophotometer. Spectra of solids were obtained using potassium bromide pellets and a film technique was used for liquid samples. Spectra were calibrated with the 1601-cm^{-1} band of a polystyrene film reference. Nmr spectra were recorded on Varian Associates A-60 or T-60 spectrometers. All proton spectra are reported in τ units relative to tetramethylsilane (TMS). Unless otherwise stated, deuteriochloroform was used as solvent. Gas chromatographic (vpc) analyses were performed on an F & M (Model 5750) research chromatograph. Two 6 ft × $^1/_8$ in. stainless steel columns were used; 10% silicone gum rubbber UC W98 on Diatoport-S (UC-W98 column) and 10% Apiezon L on Chromosorb W/AW-MCDS (Apiezon L column). Organic microanalyses were performed by Scandanavian Microanalytical Laboratories, Herlev, Denmark, and Organic Microanalyses (Dr. C. Daessle), Montreal, Canada. Trimethyl phosphite (Aldrich Chemical Co. Ltd.) was purified by prolonged treatment with molecular sieves "Linde" Type 3A (1/16) followed by fractional distillation. Tris(dimethylamino)phosphine (Eastman Kodak Chemical Co.) was used without further purification. Carbonyl compounds (benzil, biacetyl, etc.) were freshly distilled or recrystallized from aprotic solvents.

Preparation of Aromatic Sulfenyl Chlorides.—The procedure used was a modification on the method of Emde.[29] In a 500-ml flask fitted with a dropping funnel and a reflux condenser carrying a drying tube was placed *N*-chlorosuccinimide (26.7 g, 0.2 mol). Benzene (120 ml) was added and the contents of the flask were stirred magnetically to form a slurry. A solution of the aromatic thiol (0.2 mol) in benzene (50 ml) was added dropwise with the flask being cooled by ice water. An orange-red color developed after 5 min; it deepened as the addition continued. After the addition was complete, the mixture was stirred for 24 hr at room temperature. The white solid (succinimide) was removed by filtration and the deep red filtrate was concentrated under reduced pressure. Carbon tetrachloride (30 ml) was added to the red oil to precipitate the last traces of succinimide. After filtration, the filtrate was concentrated and the residual red oil distilled under reduced pressure. The yields and boiling points are given in Table III.[30a,b]

TABLE III

RCl	Yield, %	Bp, °C (mm)	Reported bp, °C (mm)
p-$CH_3C_6H_4$ (**4a**)	70	44 (0.3)	77.5–78.5 (2.5)
C_6H_5 (**4b**)	73	58 (0.8)	73–75 (9.0)
p-ClC_6H_4 (**4c**)	86	90 (0.4)	94 (6.0)

Reaction of Aromatic Sulfenyl Chlorides with the 1:1 Benzil–Trimethyl Phosphite Adduct (3a).—To a 50-ml, three-necked, round-bottomed flask fitted with a dropping funnel, gas inlet tube, and a condenser connected to a mercury trap, was added benzil (2.10 g, 0.01 mol). The flask was flushed with dry nitrogen for 15 min. Trimethyl phosphite (1.24 g, 0.01 mol) was added; an exothermic reaction occurred immediately and the pale yellow viscous liquid was stirred for 1 hr. Benzene (10 ml) was added to dissolve the syrup. This was followed by the aromatic sulfenyl chloride (0.01 mol) in benzene (10 ml). As the addition continued, the deep red color changed to pale yellow. Once the addition was complete, the reaction mixture was stirred for 1 hr at room temperature. The solvent was removed on a flash evaporator and *n*-hexane (15 ml) was added to the residue. A white crystalline solid separated on cooling and was filtered and recrystallized from *n*-hexane–benzene. The melting points, yields, and analytical data of the aromatic chloroketo sulfides are summarized in Table I. The reaction mixture showed the presence of trimethyl phosphate when compared with an authentic sample by gas chromatography using an Apiezon L column. No aromatic disulfides were detected.

Preparation of Aliphatic Sulfenyl Chlorides.—Ethane, phenyl-

(29) H. Emde, German Patent 804,572 (1951); *Chem. Abstr.*, **46**, 529 (1952).

(30) (a) H. Lecher, F. Holschneider, K. Koberle, W. Speer, and P. Stocklin, *Ber.*, **58**, 409 (1925); (b) E. Gebauer-Fulnegg, *J. Amer. Chem. Soc.*, **49**, 2270 (1927).

TABLE IV

$$R''SSR'' + Cl_2 \longrightarrow 2R''SCl$$
(0.005 mol)

Chemical shift (τ) of α methylene protons					
Disulfide		Sulfenyl chloride		Cl_2 required, g	Temp of chlorinolysis, °C
$(CH_3CH_2S-)_2$[a]	7.30	CH_3CH_2SCl (**4e**)	6.90	0.40	−30
$(C_6H_5CH_2S-)_2$[b]	6.50	$C_6H_5CH_2SCl$ (**4d**)	5.73	0.36	0–5
$(CH_3O_2CCH_2S-)_2$[b]	6.33	$CH_3O_2CCH_2SCl$ (**4f**)	5.97	0.80	0–5

[a] Neat disulfide. [b] Carbon tetrachloride (10 ml).

methane, and carbomethoxymethanesulfenyl chlorides were generated by chlorinolysis of the corresponding disulfides. The progress of the reaction was monitored by nmr. As the sulfenyl chloride was formed a significant decrease (τ 0.4–0.5) in the chemical shifts of protons α to the sulfur atom was observed. In a typical run, chlorine was passed into the disulfide (neat or a solution in CCl_4) until the nmr signal of methylene protons α to sulfur had disappeared. The experimental procedure adopted was similar to that reported for methanesulfenyl chloride.[31] Relevant reaction data are collected in Table IV.

Reaction of Aliphatic Sulfenyl Chlorides with 3a.—Adduct **3a** was generated from benzil (2.10 g, 0.01 mol) and trimethyl phosphite (1.25 g, ~0.01 mol) as described previously. The sulfenyl chloride (obtained by the chlorinolysis of 0.005 mol of the corresponding disulfide) was added dropwise to adduct **3a** in carbon tetrachloride (10 ml) at 0°. The red color of the sulfenyl chloride was discharged as the addition progressed. After 0.5–1 hr at room temperature, the solvent was removed under reduced pressure; last traces were removed using a vacuum pump. The resulting white chloro keto sulfide was recrystallized from *n*-hexane–benzene. The physical and spectroscopic data are summarized in Table I. Owing to the low stability of the chloro-keto sulfide, it was converted to the corresponding α-benzyloxy-β-keto sulfide for elemental analysis. To the reaction mixture obtained by adding sulfenyl chloride (0.01 mol) to adduct **3a** (0.01 mol) in benzene (10 ml) were added benzyl alcohol (1.10 g, 0.01 mol) and silver carbonate (1.50 g). The mixture was stirred overnight at room temperature. Silver salts were removed by filtration and the filtrate was concentrated. The α-benzyloxy-β-keto sulfide so formed was recrystallized from methanol. The analysis data are summarized in Table I.

Reaction of 2-Benzothiazolesulfenyl Chloride (4g) with 1:1 Benzil–Trimethyl Phosphite Adduct 3a.—2-Benzothiazolesulfenyl chloride (**4g**) was prepared by the action of sulfuryl chloride on 2,2′-dithiobis(benzothiazole). To a suspension of freshly recrystallized 2,2′-dithiobis(benzothiazole) (1.65 g, 0.005 mol) in methylene chloride (20 ml) at room temperature was added sulfuryl chloride (0.68 g, 0.005 mol). As the reaction progressed, the suspended disulfide dissolved and the solution turned deep red. After 1 hr at room temperature, it was added to the adduct **3a** prepared as before from benzil (2.10 g, 0.01 mol) and trimethyl phosphite (1.25 g, 0.01 mol) in benzene (10 ml). As the addition progressed, the deep red color of 2-benzothiazolesulfenyl chloride changed to pale yellow. Once the addition was complete, the reaction mixture was stirred at room temperature for 1 hr. The solvent was removed under reduced pressure and the resulting pale yellow solid was recrystallized from methylene chloride–*n*-hexane. The α-chloro-β-keto sulfide **5g** crystallized out as white plates. See Table I for physical, analytical, and spectroscopic data.

Reaction of *p*-Toluenesulfenyl Chloride (4a) with 1:1 Benzil–Tris(dimethylamino)Phosphine Adduct 3b.—In a 50-ml, three-necked, round-bottomed flask fitted with a dropping funnel, gas inlet tube, and a condenser connected to mercury trap was placed benzil (1.05 g, 0.005 mol). Dry methylene chloride (10 ml) was added to dissolve the benzil and the solution was cooled to 5°. The reaction system was flushed with dry nitrogen for 15 min. Tris(dimethylamino)phosphine (**2b**, 0.8 g, ~0.005 mol) was added dropwise with stirring. The yellow color of the solution turned deep red, and stirring was continued for 30 min at 5° after the addition was complete. *p*-Toluenesulfenyl chloride **4a** (0.8 g, 0.005 mol) in methylene chloride (10 ml) was added to the adduct **3b**. After 1 hr at room temperature, the solvent was removed under reduced pressure and *n*-hexane (10 ml) was added to the residue. On cooling, a yellowish white solid precipitated out, yield 0.8 g (45%). Recrystallization from *n*-hexane gave white needles melting at 117–118°. This product was shown to be identical with the α-chloro-β-keto sulfide **5a** obtained from the 1:1 benzil–trimethyl phosphite adduct (**3a**)–*p*-toluenesulfenyl chloride (**4a**) reaction by mixture melting point and ir. Chromatographic analysis of the mother liquor, using an Apiezon L column, revealed the presence of the α-chloro-β-keto sulfide **5a** and hexamethylphosphoramide **7**. No *p*-tolyl disulfide was detected.

Preparation of 1:1 Biacetyl–Trimethyl Phosphite Adduct 3c.—Adduct **3c** was prepared as previously described.[6] Biacetyl (14.8 g) was converted to adduct **3c**, 33.5 g (86%), bp 46° (0.6 mm) (lit.[6] 45–47° (0.5 mm)).

Reaction of Benzenesulfenyl Chloride (4b) with 1:1 Biacetyl–Trimethyl Phosphite Adduct 3c.—Adduct **3c** (2.10 g, 0.01 mol) was dissolved in carbon tetrachloride (10 ml) under dry nitrogen. The solution was cooled to 5°. Benzenesulfenyl chloride (**4b**, 1.45 g, 0.01 mol) in carbon tetrachloride (5 ml) was added dropwise. An exothermic reaction occurred with a disappearance of the red color of sulfenyl chloride **4b**. The nmr spectrum of the reaction mixture showed the following: τ 2.30–2.90 (5 H, m), 6.30 (3 H, d, J = 12 Hz), 6.22 (3 H, d, J = 12 Hz), 7.00 (3 H, s), 7.63 (3 H, s), 7.67 (3 H, s), 8.32 (3 H, s). Extensive decomposition occurred on distillation.

Reaction of Ethanesulfenyl Chloride (4e) with 1:1 Biacetyl–Trimethyl Phosphite Adduct 3c.—The above procedure was repeated using ethanesulfenyl chloride (**4e**, 0.01 mol) instead of benzenesulfenyl chloride (**4b**). The nmr spectrum of the reaction mixture showed the following: τ 6.24 (3 H, d, J = 12 Hz), 6.30 (3 H, d, J = 12 Hz), 7.00 (3 H, s), 7.62 (3 H, s), 7.67 (3 H, s), 7.82 (3 H, s), 8.07 (3 H, s), 7.10–7.90 (2 H, m), 8.40–8.93 (3 H, m). Extensive decomposition occurred on distillation.

Preparation of Biacetyl Monohydrazone.—The reported procedure for the preparation of biacetyl monohydrazone[32] has been modified as follows. A solution of biacetyl (10 ml) in benzene (10 ml) was cooled in an ice bath, and anhydrous hydrazine (3.87 g) was added dropwise with stirring. About 10 min after the addition was complete, a white solid precipitated and was filtered. The crude monohydrazone was dissolved in hot benzene and this layer decanted. On cooling, biacetyl monohydrazone crystallized, yield 7.5 g (65%), mp 64–65° (lit.[32] mp 67°).

Preparation of Azibutanone.—Two procedures were used to prepare azibutanone (diazobutanone) from biacetyl monohydrazone.

Procedure I. Using Silver Oxide.—Biacetyl monohydrazone (6.0 g) in methylene chloride (20 ml) was added to vigorously stirred suspension of silver oxide (20 g) and anhydrous sodium sulfate (20 g) in methylene chloride (80 ml). After the initial reaction had subsided, the mixture was stirred at room temperature for 24 hr. The inorganic salts were removed by filtration. The residue was washed with several portions of methylene chloride until the washings were devoid of yellow color. The washings were combined and concentrated in a flash evaporator. The residual red oil was distilled under reduced pressure using a water aspirator. The product boiling at 32° (7 mm) was collected: yield 3.0 g (51%); lit.[32] bp 45° (12–13 mm); ir 1650 (CO), 2070 cm^{-1} (N=N); nmr τ 7.85 (3 H, s), 8.22 (3 H, s).

Procedure II. Using Mercuric Oxide (Yellow).—Biacetyl monohydrazone (10.0 g) in methylene chloride (50 ml) was added to a vigorously stirred suspension of yellow mercuric oxide (22 g) and anhydrous sodium sulfate (30 g) in methylene chloride (150 ml) containing two drops of alcoholic sodium hydroxide. After the initial reaction had subsided, the mixture was stirred for 24 hr. Azibutanone was isolated by a similar work-up as in procedure I, yield 9.0 g (90%), bp 32° (7 mm).

Preparation of α-Acetyl-α-chloroethyl Phenyl Sulfide (8a).—

(31) I. B. Douglass, *J. Org. Chem.*, **24**, 2004 (1959).

(32) O. Diels and K. Pflanmer, *Ber.*, **48**, 223 (1915).

Benzenesulfenyl chloride (**4b**, 1.45 g, 0.01 mol) in carbon tetrachloride (10 ml) was added dropwise to a solution of azibutanone (0.98 g, 0.01 mol) in carbon tetrachloride (10 ml) at −10°. As the addition continued, the deep red color of the sulfenyl chloride **4b** and the orange color of azibutanone turned lighter with vigorous evolution of nitrogen. At the end of addition, a light yellow color was obtained. The solvent was removed and the residual oil distilled under reduced pressure. The α-chloro-β-keto sulfide **8a** distilled at 126° (0.005 mm) as a pale yellow oil: yield 1.7 g (80%); ir 1725 cm^{-1} (CO); nmr τ 2.20–2.70 (5 H, m), 7.62 (3 H, s), 8.21 (3 H, s). Exact mass data: calculated for $C_{10}H_{11}OSCl$, 214.0219; found, 214.0224.

Preparation of α-Acetyl-β-chloroethylethyl Sulfide 8b.—Ethyl disulfide (2.44 g, 0.02 mol) reacted at −30° with chlorine (1.42 g, 0.02 mol). The deep red ethanesulfenyl chloride **4e** was added dropwise to azibutanone (3.95 g, 0.04 mol) in carbon tetrachloride (30 ml) at −20°. As the addition continued, the color of the reaction mixture became lighter and was accompanied by the evolution of nitrogen. After the addition was complete, the solvent was removed on a flash evaporator and the residue yellow oil was distilled under reduced pressure. The α-chloro-β-keto sulfide **8b** distilled at 44° (0.1 mm) as a pale yellow oil: yield 5.6 g (84%); ir 1730 cm^{-1} (CO); nmr τ 7.30 (2 H, AB, J = 7 Hz), 7.59 (3 H, s), 8.03 (3 H, s), 8.75 (3 H, split t, J = 7 Hz). Exact mass data: calculated for $C_6H_{11}OSCl$, 166.0219; found, 166.0204. Owing to its low stability at room temperature, the product was stored in Dry Ice.

Preparation of Dimethyl Phosphorochloridate (11).—Trimethyl phosphite (7.4 g) in benzene (15 ml) was cooled in an ice bath. Chlorine gas was bubbled through the solution until it turned pale yellow. The solvent and other volatile products were removed on a flash evaporator and the residue was distilled under reduced pressure: yield 7.2 g (85%); bp 66° (10 mm) (lit.[33] bp 75–80° (20–25 mm)).

Preparation of *S*-Methylisothiuronium Dimethyl Phosphate.—This compound was prepared by a modification of the reported procedure.[34] In a 150-ml flask, fitted with a reflux condenser carrying a drying tube, were placed trimethyl phosphate (14.0 g), thiourea (7.6 g), and acetonitrile (35 ml). The reaction mixture was stirred and refluxed. The thiourea dissolved on warming and after 1.5 hr a white solid precipitated from the clear solution; refluxing was continued for another 2 hr. The reaction mixture was cooled and white crystals of *S*-methylisothiouronium dimethyl phosphate were collected, yield 17.7 g (82%), mp 139–141° (lit.[34] mp 136°).

Reaction of *p*-Toluenesulfenyl Chloride (4a) with 1:1 Benzil–Trimethyl Phosphite Adduct 3a in the Presence of 1,3,5-Trinitrobenzene as Free-Radical Inhibitor.—The adduct **3a** was generated as described previously from benzil (2.10 g, 0.01 mol) and trimethyl phosphite (1.25 g, 0.01 mol). It was dissolved in benzene (10 ml) and 1,3,5-trinitrobenzene (0.2 g) was added. The color changed to deep red. *p*-Toluenesulfenyl chloride (**4a**, 1.58 g, 0.01 mol) in benzene (5 ml) was added dropwise. At the end of the addition, the yellow reaction mixture was stirred for an additional 10 min. Benzene was removed on a flash evaporator and the residue recrystallized from *n*-hexane–methylene chloride mixture, yield 2.8 g (80%), mp 120–122°. This product was shown to be identical with α-benzoyl-α-chlorobenzyl *p*-tolyl sulfide (**5a**) by mixture melting point and ir spectra. Gas chromatographic analysis of the mother liquor on an Apiezon L column showed the presence of trimethyl phosphate and α-chloro-β-keto sulfide **5a**.

Reaction of *p*-Toluenesulfenyl Chloride (4a) with Azibenzil (26).[35]—In a 50-ml erlenmyer flask equipped with a magnetic stirrer was placed dry monoglyme (10 ml). Azibenzil (**26**, 2.22 g, 0.01 mol) was added with stirring and the resulting orange solution was cooled in an ice bath. *p*-Toluenesulfenyl chloride **4a** (1.59 g, 0.01 mol) was added dropwise to the azibenzil solution. As the addition progressed, the orange color of the azibenzil solution became lighter with evolution of nitrogen. Once the addition was complete, the pale yellow solution was stirred for 10 min at room temperature. The solvent was removed and the residue was recrystallized from *n*-hexane–methylene chloride. The yield of white crystalline product was 3.2 g (93%), mp 120–122°. This product was shown to be identical with α-benzoyl-α-chlorobenzyl *p*-tolyl sulfide **5a** by mixture melting point and ir spectra.

Reaction of Azibenzil (26) with Styrene.—A solution of **26** (4.4 g, 0.02 mol) and styrene (2.1 g, 0.02 mol) containing few crystals of 1,3,5-trinitrobenzene (polymerization inhibitor) in ether (10 ml) was heated under reflux for 41 hr. At the end of the reflux period, the solvent was removed under reduced pressure and the residual orange viscous oil was dissolved in acetic acid and cooled. The yellow crystals were separated by filtration and recrystallized from ethanol. Pale yellow crystals (3.1 g, 52%) of 2,2,3-triphenylcyclobutanone (**27**), mp 136–138°, were obtained. This product on further recrystallization from *n*-hexane–methylene chloride yielded white crystals melting at 137–138° (lit.[23] mp 132–136°); ir 1775 cm^{-1} (CO); nmr τ 2.20–3.20 (15 H, m), 5.47 (2 H, split t, J = 9 Hz), 6.50 (2 H, d, J = 9 Hz).

Attempted Reaction of 1:1 Benzil–Trimethyl Phosphite Adduct 3a with Styrene.—The adduct **3a** was generated as described previously from benzil (2.10 g, 0.01 mol) and trimethyl phosphite (1.25 g, 0.01 mol). It was dissolved in dry ether (10 ml) and styrene (1.05 g, 0.01 mol) containing a few crystals of 1,3,5-trinitrobenzene. The reaction mixture was refluxed for 41 hr and monitored by gas chromatography using Apiezon L and UCW-98 columns and by tlc on silica gel using 1:1 methylene chloride–hexane as eluent. The analysis of the reaction mixture showed the absence of 2,2,3-triphenylcyclobutanone (**27**).

Registry No.—**3a**, 4850-55-9; **3b**, 7137-83-9; **3c**, 1665-79-8; **4a**, 933-00-6; **4b**, 931-59-9; **4c**, 933-01-7; **4d**, 26826-81-3; **4e**, 1496-75-9; **4f**, 33537-30-3; **5a**, 28220-62-4; **5b**, 28194-60-7; **5c**, 28194-61-8; **5d**, 28194-62-9; **5e**, 28194-63-0; **5f**, 33537-32-5; **5g**, 28194-65-2; **8a**, 33487-46-6; **8b**, 33487-47-7; **26**, 3469-17-8; biacetyl monohydrazone, 33487-48-8; azibutanone, 14088-58-5.

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(33) G. M. Kosalapoff, "Organo Phosphorus Compounds," Wiley, New York, N. Y., 1950, p 252.

(34) J. B. Parker and T. D. Smith, *J. Chem. Soc.*, 442 (1961).

(35) Azibenzil (diazobenzil) was prepared according to the procedure of A. I. Vogel, in "A Textbook of Practical Organic Chemistry," Longmans, Green and Co. London, 1964, p 856.

Photochemical and Thermal Transformations of O-Alkyl S-Phthalidyl Xanthates and Dithiocarbamoyl Phthalides

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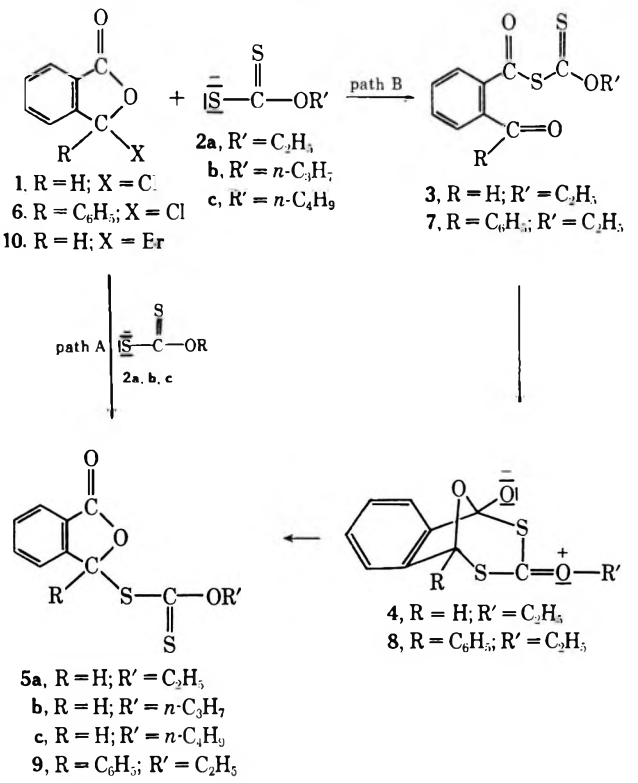
The reaction of 3-chlorophthalide, 3-bromophthalide, and 3-chloro-3-phenylphthalide with potassium O-alkyl xanthates gave the corresponding O-alkyl S-(3-phthalidyl) xanthates. Dithiocarbamates, on the other hand, gave the corresponding 3-dithiocarbamoyl phthalides. Photolysis of both O-alkyl S-(3-phthalidyl) xanthates and 3-dithiocarbamoyl phthalides gave *meso*-dihydrobiphthalide as the chief product in each case. The thermal decomposition of these substances, on the other hand, gave a mixture of products consisting of carbonyl sulfide, thiophthalic anhydride, 3,3′-monothiobiphthalide, 3,3′-dithiobiphthalide, and isocoumarino[4,3-*c*]isothiocoumarin. The thermal and photochemical decomposition of O-ethyl S-(3-phenylphthalidyl) xanthate gave rise to 3,3′-diphenylbiphthalide as the chief product. The same product was obtained from the thermal and photochemical decompositions of 3-dithiocarbamoyl-3-phenylphthalides.

In earlier communications[2,3] we had reported the reactions of both symmetrical and unsymmetrical phthaloyl dichlorides with several potassium O-alkyl xanthates and dithiocarbamates which led to the synthesis of phthaloyl dixanthates and bisdithiocarbamic anhydrides. In the reaction of symmetrical phthaloyl dichloride with potassium O-methyl xanthate, for example, the unsymmetrical di-O-methyl S,S-phthaloyl dixanthate was formed as the major product. It was shown that in this reaction the symmetrical di-O-methyl S,S-phthaloyl dixanthate is formed initially which then rapidly rearranges to the unsymmetrical isomer. The reaction of dithiocarbamates with both symmetrical and unsymmetrical phthaloyl dichlorides, on the other hand, gave the corresponding symmetrical phthaloic bisdithiocarbamic anhydrides, in each case. In continuation of our studies, we have examined the reactions of a few monohalophthalides with potassium O-alkyl xanthates and dithiocarbamates, with a view to examining the nature of the products formed in these reactions.

Treatment of potassium O-ethyl xanthate with an acetone solution of 3-chlorophthalide (**1**) gave a product which was identified as O-ethyl S-phthalidyl xanthate (**5a**), mp 107–108°. The identity of this product was confirmed on the basis of analytical results and spectral data. The ir spectrum of **5a** showed a carbonyl absorption at 1770 cm^{-1}, characteristic of a γ-lactone. The nmr spectrum of **5a** showed a multiplet centered around δ 7.9 (5 H) due to the four aromatic protons and one tertiary proton attached to the 3 position of the phthalide nucleus. In addition, the spectrum showed a quartet centered around δ 4.89 (2 H) due to the methylene protons and a triplet at δ 1.42 (3 H) due to the methyl protons of the alkyl side chain.

The formation of **5a** may be rationalized in terms of a direct displacement of the chloride ion (path A) or through the attack of the nucleophile on the carbonyl carbon (path B) as shown in Scheme I. If the reaction is proceeding through path B, then one would expect the formation of the intermediate aldehydo xanthate **3**, which can then rearrange to **5a** through a bicyclo[3.2.1] transition state **4**.[4] With a view to finding out

SCHEME I



whether the intermediate **3** is formed in the reaction or not, we have examined the absorption spectrum of the product mixture, immediately after mixing together the chlorophthalide **1** and potassium O-ethyl xanthate in a 1:1 ratio, in acetone solution around 5°. The absorption spectrum of this mixture was characterized by the presence of a maximum at 390 nm (ε 80), characteristic of acyl and aroyl xanthates containing the –C(=O)SC(=S)– chromophore.[2,3,5] Further, it was observed that the absorption maximum at 390 nm of a freshly formed solution of **3** gradually disappeared, and a new absorption maximum at 362 nm (ε 50) was observed due to the formation of **5a**. In this connection it might be mentioned that a similar absorption maximum around 360 nm was observed in all the unsymmetrical phthaloyl dixanthates that we have ex-

(1) To whom enquiries should be addressed.

(2) A. Shah, S. N. Singh, and M. V. George, *Tetrahedron Lett.*, 3983 (1968).

(3) S. N. Singh and M. V. George, *J. Org. Chem.*, **36**, 615 (1971).

(4) For some examples involving bicyclo[3.2.1] transition states, see (a) ref 3; (b) M. S. Newman and C. Courduvelis, *J. Amer. Chem. Soc.*, **86**, 2942 (1964); **88**, 781 (1966); (c) M. S. Newman, N. Gill, and B. Darre, *J. Org. Chem.*, **31**, 2713 (1966); (d) M. S. Newman and L. K. Lala, *ibid.*, **32**, 3225 (1967); (e) M. S. Newman, S. S. Gupte, and S. Sankarappa, *ibid.*, **35**, 2757 (1970).

(5) D. H. R. Barton, M. V. George, and M. Tomoeda, *J. Chem. Soc.*, 1967 (1962).

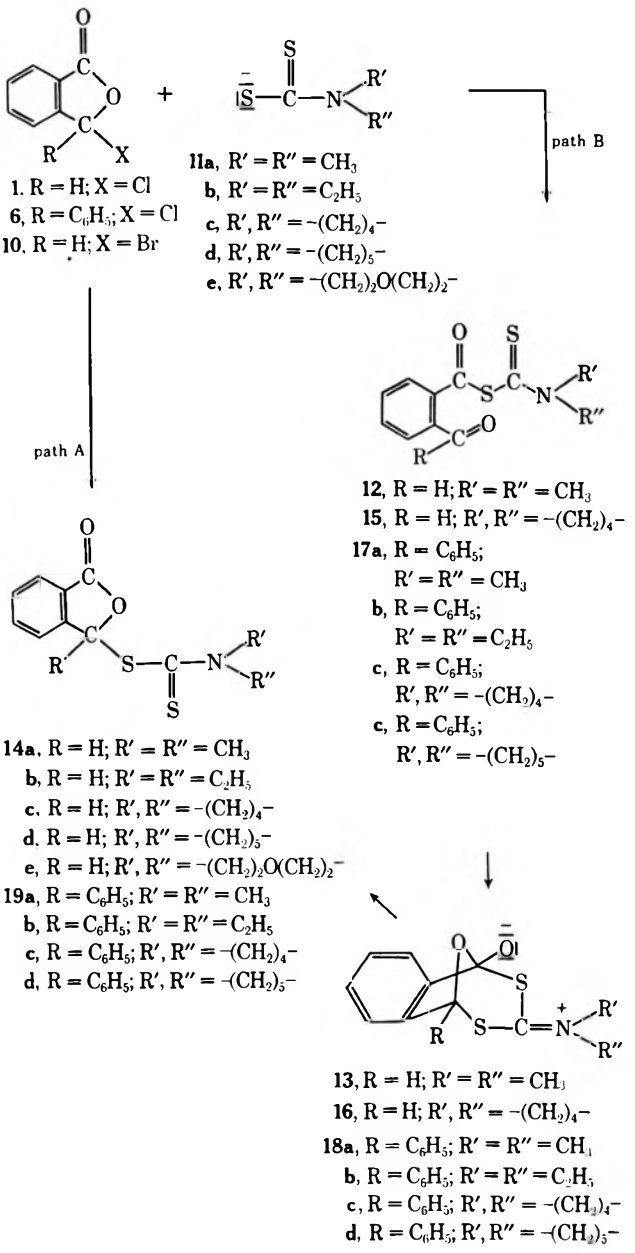
amined earlier.[3] These observations support the view that the reaction of **1** with potassium *O*-ethyl xanthate proceeds through B, as shown in Scheme I.

With a view to studying the mode of displacement in a few other phthalide derivatives, we have examined the reactions of 3-chloro-3-phenylphthalide and 3-bromophthalide with different potassium *O*-alkyl xanthates. Treatment of potassium *O*-ethyl xanthate with an acetone solution of 3-chloro-3-phenylphthalide (**6**), for example, gave a 60% yield of *O*-ethyl *S*-(3-phenylphthalidyl) xanthate (**9**), mp 88°. It has been observed that a freshly formed solution of **9** shows an absorption maximum at 392 nm (ϵ 75), characteristic of the –C(=O)SC(=S)– chromophore present in the intermediate xanthate **7** (Scheme I). The absorption maximum at 392 nm gradually disappeared, and a new absorption band was observed at 366 nm, characteristic of the rearranged xanthate **9**. It is therefore inferred that the reaction of potassium *O*-ethyl xanthate with **6** proceeds through path B (Scheme I) and is similar to the reaction of 3-chlorophthalide. The reaction of potassium *O*-ethyl xanthate with 3-bromophthalide (**10**), on the other hand, gave rise to a 88% yield of **5a**. It is interesting to note that, even when this reaction was carried out at low temperatures (−30°), we could not detect the formation of any aldehydo xanthate (**3**). It appears that the nucleophilic substitution in this case is proceeding through path A, involving a direct displacement of the halide ion. This difference in the mode of reactions between 3-chlorophthalide and 3-bromophthalide may be attributed to the greater ease with which benzyl bromides undergo displacement reactions when compared to the corresponding chlorides. Similarly, the reactions of potassium *O*-*n*-propyl xanthate and potassium *O*-*n*-butyl xanthate with **10** resulted in the formation of *O*-*n*-propyl *S*-(3-phthalidyl) xanthate (**5b**) and *O*-*n*-butyl *S*-(3-phthalidyl) xanthate (**5c**) in 80 and 75% yields, respectively.

Our next objective was to examine the reactions of 3-chlorophthalide, 3-chloro-3-phenylphthalide, and 3-bromophthalide with different dithiocarbamates with a view to studying the nature of the products formed in these reactions. The reaction of 3-chlorophthalide (**1**) with dimethyldithiocarbamate (**11a**), for example, gave a 62% yield of a product, mp 186–187°, identified as 3-[(dimethylthiocarbamoyl)thio]phthalide (**14a**), based on analytical results and spectral data. The ir spectrum of **14a** showed an absorption band at 1750 cm^{-1}, characteristic of a γ-lactone carbonyl group. The uv spectrum of **14a** showed an absorption maximum at 340 nm (ϵ 90), characteristic of unsymmetrical phthaloic dithiocarbamic anhydrides.[3] The nmr spectrum of **14a** showed a multiplet centered around δ 7.9 (5 H) due to the four aromatic protons and the tertiary proton attached to the 3 carbon of the phthalide nucleus. In addition, the spectrum showed two singlets at δ 3.42 (3 H) and 3.63 (3 H), respectively, due to the two methyl groups of the dithiocarbamate group. The magnetic nonequivalence of these two methyl groups is attributed to the restricted rotation about the C–N bond in **14a**, similar to the restricted rotation that is observed in amides.[6] Further, it was observed that

(6) For some relevant examples for the restricted rotation in amides, see (a) W. D. Phillips, *J. Chem. Phys.*, **23**, 1363 (1955); (b) H. S. Gutowsky and C. H. Holm, *ibid.*, **25**, 1228 (1956).

SCHEME II



the two separate peaks appearing at δ 3.42 and 3.63 coalesced to a single broad peak (δ 3.5) when the nmr spectrum was determined at 60°.

As in the case of the reaction of 3-chlorophthalide (**1**) with potassium *O*-ethyl xanthate, a freshly mixed solution of **1** and dimethyldithiocarbamate showed an absorption maximum at 394 nm (ϵ 100), characteristic of the –C(=O)SC(=S)– chromophore. Further, it was observed that the absorption band at 394 nm disappeared on keeping the solution at room temperature for a couple of hours, and a new absorption maximum at 340 nm (ϵ 90), characteristic of thiocarbamoyl phthalides, was observed. The initial appearance of the absorption maximum at 394 nm is attributed to the formation of the unstable benzoic dithiocarbamic anhydride intermediate **12** which then rapidly rearranges to **14a** through the bicyclo[3.2.1] transition state **13**, as shown in Scheme II (path B).

Similarly, the reaction of tetramethylenedithiocarbamate (**11c**) with **1** gave rise to a 64% yield of 3-[(tetramethylenethiocarbamoyl)thio]phthalide (**14c**).

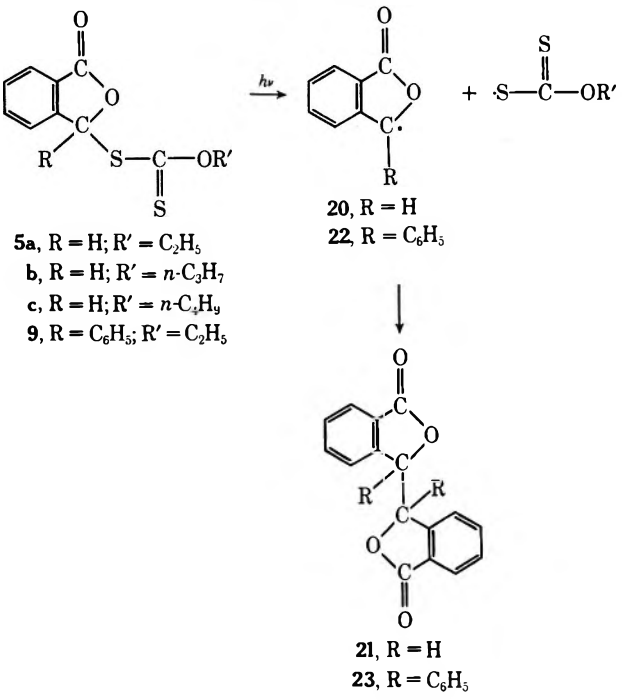
In the reaction of 3-chloro-3-phenylphthalide (**6**) with dimethyldithiocarbamate, a 60% yield of 3-phenylphthalidyl dimethyldithiocarbamate (**19a**) was formed as the chief product. Based on the appearance of an absorption maximum at 392 nm (ϵ 150) in a freshly mixed solution of **6** and **11a**, it has been inferred that this reaction proceeds through path B, as shown in Scheme II. Similarly, the reaction of diethyldithiocarbamate (**11b**), tetramethylenedithiocarbamate (**11c**), and pentamethylenedithiocarbamate (**11d**) with **6** gave rise to the corresponding phthalides, **19b**, **19c**, and **19d**, in yields ranging between 57 and 71%.

In continuation of our studies we have examined the reaction of 3-bromophthalide (**10**) with several dithiocarbamates to ascertain whether these reactions are analogous to those of *O*-alkyl xanthates. Treatment of an acetone solution of **10** with dimethyldithiocarbamate, for example, gave a 86% yield of **14a** as the only isolable product. The formation of **14a** in this reaction could arise by either a direct displacement of the bromide ion as per path A or through the attack on the carbonyl carbon as in path B (Scheme II). In order to distinguish between these two possible modes, we have examined the uv spectrum of the product mixture, immediately after mixing **10** and **11a** in acetone solution at 5°. The uv spectrum showed an absorption at 340 nm, characteristic of thiocarbamoyl phthalides, indicating thereby that the displacement reaction is proceeding through path A, as shown in Scheme II. Similarly, the reactions of **10** with diethyldithiocarbamate (**11b**), tetramethylenedithiocarbamate (**11c**), pentamethylenedithiocarbamate (**11d**), and oxydiethylenedithiocarbamate (**11e**) gave the corresponding 3-[(dialkylthiocarbamoyl)thio]phthalides, **14b–e**, in yields ranging from 75 to 85%.

Earlier we had reported the thermal and photochemical fragmentations of several unsymmetrical phthaloyl dixanthates and symmetrical phthaloic bisdithiocarbamic anhydrides.[2,3] Photolysis of unsymmetrical phthaloyl dixanthates in benzene solution, for example, gave chiefly *trans*-biphthalide, whereas symmetrical phthaloic bisdithiocarbamic anhydrides gave a mixture of *trans*-diphthalide and the corresponding thiuram disulfides. The thermal decomposition of unsymmetrical phthaloyl dixanthates, on the other hand, yielded a mixture of several products, consisting of *trans*-diphthalide, thiophthalic anhydride, carbonyl sulfide, and the corresponding *O,S*-dialkyl xanthates. During the course of the present investigation, we have examined both the thermal and photochemical transformations of several *O*-alkyl *S*-(3-phthalidyl) xanthates and 3-[(dialkylthiocarbamoyl)thio]phthalides with a view to studying the mode of these transformations.

Photolysis of *O*-ethyl *S*-(3-phthalidyl) xanthate (**5a**) in benzene solution at room temperature gave a 25% yield of *meso*-dihydrobiphthalide (**21**), mp 270°, as the only isolable product. Under analogous conditions, the photolysis of *O*-*n*-propyl *S*-(3-phthalidyl) xanthate (**5b**) and *O*-*n*-butyl *S*-(3-phthalidyl) xanthate (**5c**) gave **21** in 20 and 35% yields, respectively. The formation of *meso*-dihydrobiphthalide (**21**) in the photolysis of *O*-alkyl *S*-(3-phthalidyl) xanthates suggests that the photofragmentation reactions may be proceeding through the initial scission of a C–N bond, leading to the formation of phthalidyl radical **20**, which then dimerizes to **21** as shown in Scheme III. A similar type of photochemical fragmentation of the C–S bond is reported in the case of unsymmetrical phthaloyl dixanthates[2,3] and 9,9-dixanthogenyl xanthene.[7]

SCHEME III



If the photochemical transformation of **5a** to **21** is proceeding through a homolytic C–S bond fission, then one would expect that this process would be more facile in the case of a compound such as *O*-ethyl *S*-(3-phenylphthalidyl) xanthate (**9**), as the intermediate 3-phenylphthalidyl radical (**22**) would be more stable when compared to **20**. In accord with this view, we found that a benzene solution of **9** undergoes very ready photolysis giving rise to a 50% yield of *meso*-3,3′-diphenylbiphthalide.[8,9]

The thermal decomposition of *O*-alkyl *S*-phthalidyl xanthates is of interest in that a mixture of several products is formed in these cases. Heating a sample of *O*-ethyl *S*-phthalidyl xanthate (**5a**), for example, to *ca.* 230–240° for *ca.* 20 min gave rise to a mixture of products consisting of a 33% yield of carbonyl sulfide (**26**), identified through its piperidinium salt,[10] a 14% yield of phthalic thioanhydride (**32**), and a yellow product, mp 324–325°. Both analytical results and the presence of two molecular ion peaks at *m/e* 280 and 296, respectively, in the mass spectrum indicated that this mixture consists of compounds having the molecular formulas $C_{16}H_8O_3S$ and $C_{16}H_8O_2S_2$. The ir spectrum of this product showed four distinct carbonyl absorption bands at 1786, 1736, 1695, and 1647 cm^{-1}, indicating the presence of γ- and δ-lactones and thiolactones.[11] The uv spectrum of this mixture showed several absorption maxima, indicating that the

(7) A. Schönberg and U. Sodtke, *Tetrahedron Lett.*, 4977 (1967).

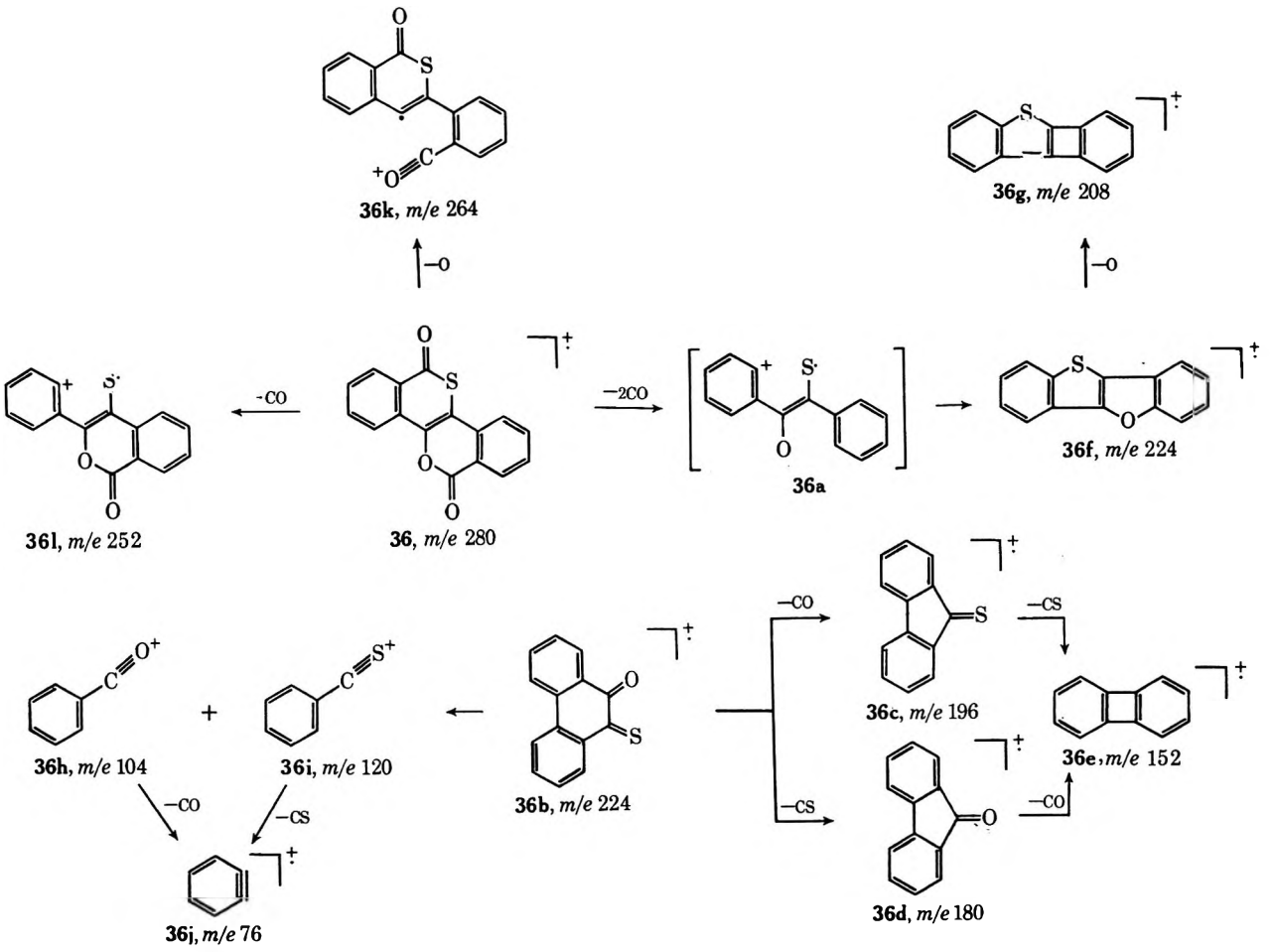
(8) On the basis of analogy to **21**, the meso configuration is assigned to **23**.

(9) For an earlier report on the formation of 3,3,-diphenylbiphthalide, see M. Renson, *Bull. Soc. Chim. Belg.*, **70**, 77 (1961); *Chem. Abstr.*, **55**, 18852 (1961).

(10) J. Parrod, *C. R. Acad. Sci.*, 234 (1952); *Chem. Abstr.*, **47**, 1606 (1953).

(11) J. H. Markgraf, C. I. Heller, and H. L. Avery, III, *J. Org. Chem.*, **35**, 1588 (1970).

SCHEME IV



components are extensively conjugated. The extreme insolubility of this mixture in most of the common organic solvents has prevented a satisfactory separation into its components. However, when a dilute solution of this product in methylene chloride was tested on a tlc plate, we could detect the presence of at least three components. It might be mentioned in this connection that Markgraf and coworkers[11] have reported the formation of a similar reaction mixture when they treated phthalic thioanhydride with tris(dimethylamino)phosphine. A similar mixture of products is also reported to be formed in the reaction of triethyl phosphite with a mixture of phthalic thioanhydride and phthalic anhydride.[12] Comparison of Markgraf's reaction mixture[13] with ours on a tlc plate indicated that two of the components, namely, 2-thio-3,3′-biphthalide (**35**) and isocoumarino[4,3-c]isothiocoumarin (**36**), were common constituents. Further confirmation of the identities of these compounds has been made by separating both the constituents **35** and **36** from our reaction mixture, employing preparative tlc and comparing their ir and uv spectra with those of the authentic samples.[13,14]

Additional evidence concerning the structure of **36** was derived from electron impact studies. The mass spectrum of **36** showed the molecular ion peak at *m/e* 280. Other peaks were observed at *m/e* 264, 252, 224, 196, 180, 152, 120, 104, and 76, which could be due to some of the fragments shown in Scheme IV. The species at *m/e* 224, 196, 180, and 152 are formulated as ions corresponding to monothiophenanthrenequinone (**36b**), thiofluorenone (**36c**), fluorenone (**36d**), and biphenylene (**36e**), respectively. The occurrence of the *m/e* 208 species is assigned to the fragment **36g**, which is probably formed by the loss of two molecules of carbon monoxide from **36**. Other peaks at *m/e* 120, 104, and 76 could be due to the fragments **36i**, **36h**, and **36j**, respectively. A peak at *m/e* 252 may be assigned to the fragment **36l**, arising through a loss of carbon monoxide from **36**, whereas the peak at *m/e* 264 could be assigned to the fragment **36k**, formed by the loss of an oxygen atom from **36**, as shown in Scheme IV. It might be mentioned in this connection that an analogous mode of fragmentation has been observed in the case of both biphthalide and bithiophthalide.[14b]

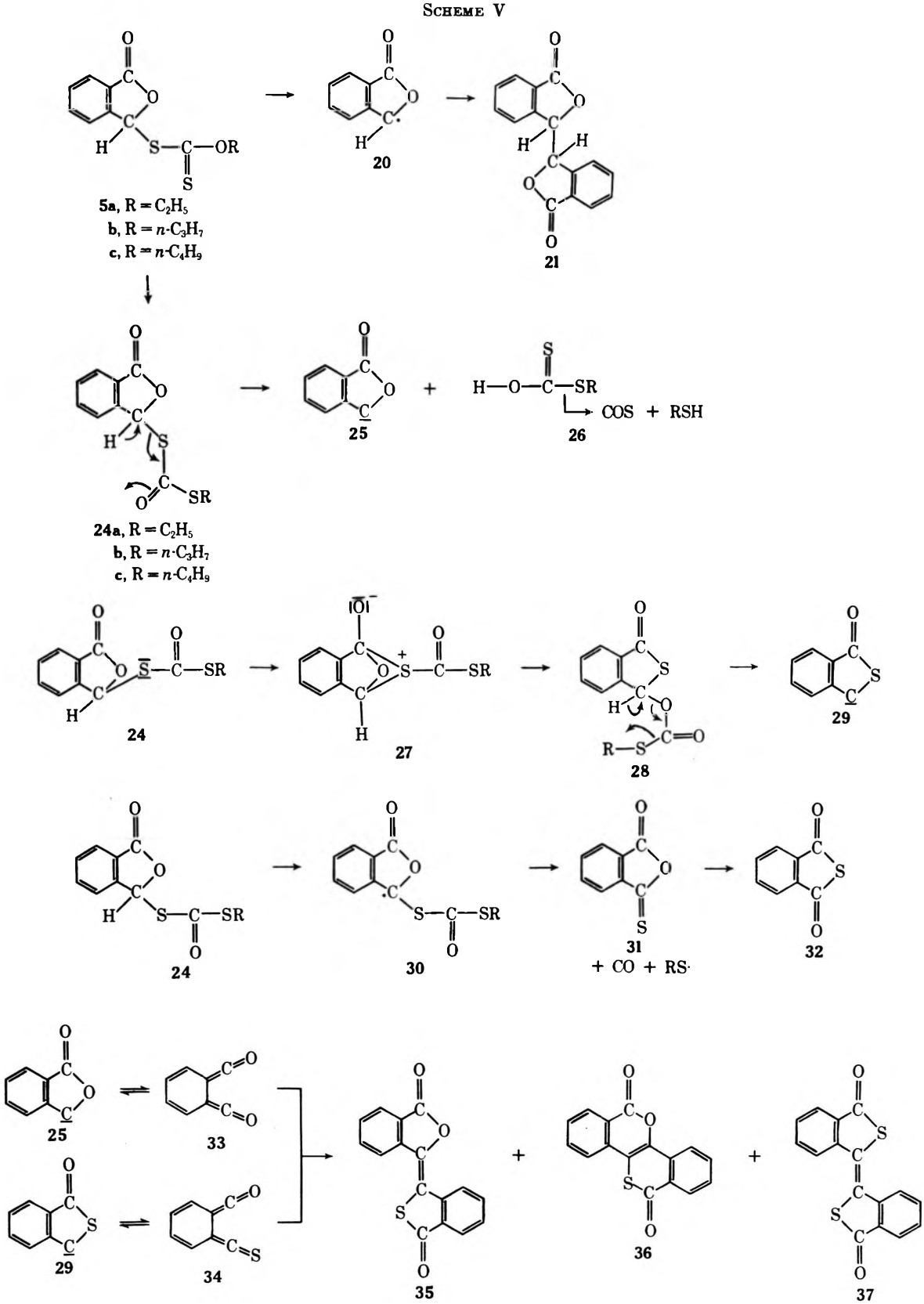
The exact mode of formation of the products **26**, **32**, **35**, **36**, and **37** in the thermal decomposition of **5a** is not very clear. A probable route to the formation of these products is indicated in Scheme V. In this scheme, we assume that the products such as 2-thio-3,3′-biphthalide (**35**), isocoumarino[4,3-c]isothiocoumarin (**36**), and 2,2′-dithio-3,3′-diphthalide (**37**) are formed from the reaction between the two carbene intermediates **25** and **29**, which can exist in equilibrium

(12) C. W. Bird and D. Y. Wong, *Chem. Commun.*, 932 (1969).

(13) We thank Dr. J. H. Markgraf for very kindly sending us a sample of the mixture of products obtained from the reaction of phthalic thioanhydride with tris(dimethylamino)phosphine.[11]

(14) (a) We thank Dr. C. W. Bird, who has kindly sent us the spectral data of compound **35**, which he obtained by extensive fractional recrystallization of a product formed in the reaction of phthalic thioanhydride with tris(dimethylamino)phosphine;[11] (b) C. W. Koch and J. H. Markgraf, *J. Heterocycl. Chem.*, **8**, 225 (1971).

SCHEME V



with their diketene isomers **33** and **34**, respectively.[15] The formation of the carbene **25** may occur through a free-radical process involving the intermediate **20** or through a cyclic concerted process involving **24a**, which in itself is a rearranged product of **5a**.[16] The decomposition of **24a** as in this scheme would also account for the formation of carbonyl sulfide, which has been identified as one of the products in the thermal decomposition of **5a**. The formation of the carbene **29**, on the other hand, is postulated through a concerted process involving the decomposition of **28**, which is

(15) For some examples of such dimerizations, see (a) R. F. C. Brown and R. K. Solly, *Tetrahedron Lett.*, 169 (1966); (b) H. A. Staab and J. Ipaktschi, *ibid.*, 583 (1966).

(16) For some examples of this type of rearrangement, see T. Taguchi and H. Nakao, *Tetrahedron*, **18**, 245 (1962).

presumed to be a transformation product of **24** and involving the bicyclo[2.2.1] transition state **27**. The occurrence of phthalic thioanhydride in this reaction may be rationalized in terms of the free-radical intermediate **30**, which can fragment further to give the thionphthalic anhydride (**31**), and the rearrangement of **31** leads to **32**.[17]

Similarly, the thermal decompositions of *O*-*n*-propyl *S*-phthalidyl xanthate (**5b**) and *O*-*n*-butyl *S*-phthalidyl xanthate (**5c**) gave carbonyl sulfide, phthalic thioanhydride, and a mixture of products consisting of **35**, **36**, and **37** in each case.

The thermal decomposition of *O*-ethyl *S*-(3-phenylphthalidyl) xanthate (**9**), on the other hand, gave a 76% yield of 3,3′-diphenylbiphthalide (**23**) as the only isolable product. A probable route to the formation of **23** is through the radical intermediate **22**, arising through a homolytic fragmentation of **9** (Scheme III). It is interesting to note that both the thermal and photochemical transformations of **9** lead to the same product **23**. The relative stabilities of the phthalidyl radicals **20** and **22** would account for the difference in behavior between the thermal decompositions of **5a** and **9**.

The C–S type of bond fission occurring in the photolysis of acyl and aroyl xanthates has also been postulated in the photofragmentation of dithiocarbamic anhydrides.[3,18] In the photolysis of symmetrical bispyrrolidine dithiocarbamic anhydride, for example, a mixture of *trans*-biphthalide and bis(tetramethylene)-thiuram disulfide are formed. The formation of these products has been explained in terms of a homolytic fragmentation of the C–S bond leading to radical intermediates.

During the course of the present investigation we have examined both the thermal and photochemical transformations of 3-[(dialkylthiocarbamoyl)thio]-phthalides with a view to studying the nature of the products formed in these reactions. Photolysis of a benzene solution of 3-[(dimethylthiocarbamoyl)thio]-phthalide (**14a**), for example, gave a 27% yield of *meso*-3,3′-dihydrobiphthalide (**21**) as the only isolable product. Similarly, the photolysis of 3-[(diethylthiocarbamoyl)thio]phthalide (**14b**), 3-[(tetramethylenethiocarbamoyl)thio]phthalide (**14c**), 3-[(pentamethylenethiocarbamoyl)thio]phthalide (**14d**), and 3-[(oxydiethylenethiocarbamoyl)thio]phthalide (**14e**) gave **21** in each case and in yields ranging between 25 and 40%. The photolysis of 3-phenylphthalidyl dimethyldithiocarbamate (**19a**), on the other hand, gave a 50% yield of 3,3′-diphenylbiphthalide (**23**). Similarly, the photolysis of 3-phenylphthalidyl diethyldithiocarbamate (**19b**), 3-phenylphthalidyl tetramethylenedithiocarbamate (**19c**), and 3-phenylphthalidyl pentamethylenedithiocarbamate (**19d**) gave, in each case, **23** in yields ranging between 45 and 57%.

The formation of 3,3′-dihydrobiphthalide (**21**) in the photolysis of 3-[(dialkylthiocarbamoyl)thio]phthalides **14a–e** and 3,3′-diphenylbiphthalide (**23**) in the photolysis of 3-phenylphthalidyl dialkyldithiocarbamates **19a–d** may be rationalized in terms of the initial C–S bond fission leading to the generation of the phthalide radicals **20** and **22**, respectively, through reaction paths similar to those indicated in Scheme III.

The thermal decomposition of the 3-[(dialkylthiocarbamoyl)thio]phthalides **14a–e** gave, in each case, a mixture of products consisting of 2-thio-3,3′-diphthalide (**35**), isocoumarino[4,3-*c*]thiosocoumarin (**36**), and 2,2′-dithio-3,3′-biphthalide (**37**) in yields ranging between 12 and 17%. The formation of the mixture of products consisting of **35**, **36**, and **37** in these cases indicates that both *O*-alkyl *S*-phthalidyl xanthates and 3-[(dialkylthiocarbamoyl)thio]phthalides undergo a similar type of thermal transformation.

The thermal decomposition of 3-phenylphthalidyl dialkyldithiocarbamates **19a–d** gave, in each case, 3,3′-diphenylbiphthalide in yields ranging between 60 and 80%. It is interesting to note that, as in the case of *O*-ethyl *S*-(3-phenylphthalidyl) xanthate, both the thermal and photochemical transformations of 3-phenylphthalidyl dialkyldithiocarbamates give rise to the same product, in each case.

Experimental Section

All melting points are uncorrected and were taken on a Mel-Temp melting point apparatus. Infrared spectra were taken on a Perkin-Elmer Model 137 Infracord spectrometer and uv spectra were determined on a Beckman DB spectrometer. The nmr spectra were determined either on a Varian A-60D or HR-100 spectrometer, using tetramethylsilane as an internal standard.

All irradiation experiments were carried out using a Hanovia medium-pressure mercury lamp (450 W).

Starting Materials.—Potassium *O*-ethyl xanthate, mp 185–186°, potassium *O*-*n*-propyl xanthate, mp 237–238°, and potassium *O*-*n*-butyl xanthate, mp 261–262°, were prepared by known procedures.[19] Dimethyldithiocarbamate,[20] mp 136°, diethyldithiocarbamate,[20] mp 152°, tetramethylenedithiocarbamate,[18] mp 152°, pentamethylenedithiocarbamate,[18] mp 169–170°, and oxydiethylenedithiocarbamate,[18] mp 180–182°, were prepared by reported procedures. 3-Chlorophthalide,[21] mp 61°, 3-bromophthalide,[22] mp 78–80°, and 3-chloro-3-phenylphthalide,[23] mp 60°, were prepared in good yields as per standard reports.

Reaction of 3-Chlorophthalide (1) with Potassium *O*-Ethyl Xanthate (2a).—To a solution of **1** (0.42 g, 0.0025 mol) in acetone (20 ml), maintained around 5°, was gradually added **2a** (0.4 g, 0.0025 mol) in small portions and with constant stirring. After removal of the solvent from the reaction mixture, the residue was treated with excess of water to remove any unchanged **2a** and recrystallized from a mixture (1:1) of ethanol and methylene chloride to give 0.42 g (66%) of *O*-ethyl *S*-(3-phthalidyl) xanthate (**5a**), mp 107–108°.

Anal. Calcd for $C_{11}H_{10}O_3S_2$: C, 51.96; H, 3.93. Found: C, 52.59; H, 4.03.

The ir spectrum (KBr) of **5a** showed an absorption band at 1770 cm^{-1} due to the carbonyl group (γ-lactone) and another band at 1040 cm^{-1} due to the C=S group.

The uv spectrum of **5a**(CH_2Cl_2) was characterized by the following absorption maxima: 278 nm (ε 12,600) and 362 (50).

Reaction of 3-Bromophthalide (10) with Potassium *O*-Alkyl Xanthates (2a–c).—In a typical run, a solution of **2a** in acetone (0.019 mol in 25 ml) was slowly added to an acetone solution of **10** (0.018 mol in 25 ml), maintained around 5°. The addition was completed in about 30 min, during which period the mixture was kept stirred. Removal of the solvent under vacuum and treatment of the residue with water to remove any unchanged **2a** gave a 88% yield of **5a**, mmp 107–108°.

Under similar conditions, the reaction of **10** with **2b** gave a 80% yield of *O*-*n*-propyl *S*-(3-phthalidyl) xanthate (**5b**), mp

(17) For examples of this type of transformation, see C. M. Sharts and D. W. Fong, *J. Org. Chem.*, **32**, 3709 (1967).

(18) E. H. Hoffmeister and D. S. Tarbell, *Tetrahedron*, **21**, 35, 2857, 2865 (1965).

(19) I. S. Shupe, *J. Ass. Offic. Agr. Chem.*, **25**, 495 (1942); *Chem. Abstr.*, **36**, 4670 (1942).

(20) R. H. Sahasrabudhey and K. L. Radhakrishnan, *J. Indian Chem. Soc.*, **31**, 853 (1954).

(21) S. Gabriel, *Ber.*, **49**, 1612 (1916).

(22) I. A. Koten and R. J. Sauer, "Organic Syntheses," Vol. 42, V. Boekelhide, Ed., Wiley, New York, N. Y., 1962, p 26.

(23) H. C. Martin, *J. Amer. Chem. Soc.*, **38**, 1143 (1916).

92°, after recrystallization from a mixture (1:1) of ethanol and methylene chloride.

Anal. Calcd for $C_{12}H_{12}O_3S_2$: C, 53.73; H, 4.47. Found: C, 53.46; H, 4.38.

The ir spectrum (KBr) of **5b** showed absorption bands at 1770 (C=O, γ-lactone) and 1050 cm^{-1} (C=S).

The uv spectrum (CH_2Cl_2) of **5b** was characterized by the following absorption maxima: 278 nm (ε 12,800) and 364 (50).

In an analogous manner, the reaction of **10** with **2c** gave a 75% yield of *O*-*n*-butyl *S*-(3-phthalidyl) xanthate (**5c**), mp 90°, after recrystallization from a mixture (1:1) of ethanol and methylene dichloride.

Anal. Calcd for $C_{13}H_{14}O_3S_2$: C, 55.31; H, 4.96. Found: C, 55.20; H, 4.68.

The ir spectrum (KBr) of **5c** showed absorption bands at 1765 and 1040 cm^{-1} due to the C=O group (γ-lactone) and the C=S group, respectively.

The uv spectrum of **5c** (CH_2Cl_2) showed the following absorption maxima: 278 nm (ε 15,850) and 364 (130).

Photolysis of *O*-Alkyl *S*-(3-Phthalidyl) Xanthates.—In a representative run, a solution of **5a** (1.0 g, 0.004 mol) in benzene (200 ml) was irradiated for 30 min at room temperature. Removal of the solvent under vacuum gave a product which on treatment with a small quantity of acetone gave 0.13 g (25%) of *meso*-3,3′-dihydrobiphthalide (**21**), which melted at 270° (lit.[24] mp 269°), on recrystallization from acetic acid.

Anal. Calcd for $C_{16}H_{10}O_4$: C, 72.18; H, 3.76. Found: C, 72.33; H, 4.04.

The ir spectrum (KBr) of **21** showed an absorption band at 1765 cm^{-1} due to a γ-lactone carbonyl group.

The uv spectrum (CH_2Cl_2) of **21** showed the following absorption maxima: 238 nm (ε 1350), 276 (3650), 284 (3750), 296 (900), 308 (900), 362 (2050), 376 (1680), and 384 (1450).

In identical runs, the photolysis of **5b** and **5c** gave **21** in 20 and 35% yields, respectively.

Thermal Decomposition of *O*-Alkyl *S*-(3-Phthalidyl) Xanthates.—In a typical run, 4.0 g (0.016 mol) of **5a** was heated at *ca.* 230–240° for 20 min in a 10-ml round-bottomed flask provided with a nitrogen inlet and a water-cooled condenser. The gaseous products were bubbled through a 10% solution of piperidine in diethyl ether. The precipitated piperidinium salt was filtered and recrystallized from a mixture (1:1) of methylene chloride and diethyl ether to give 1.2 g (33%) of piperidinium 1-piperidine carbothiolate, mp 112°, which showed no depression in its melting point when mixed with an authentic sample.[9]

The pyrolyzed mixture was extracted with methylene chloride to give a methylene chloride soluble fraction, which after removal of the solvent and recrystallization from a mixture (1:1) of methylene chloride and petroleum ether (bp 60–80°) gave 0.35 g (14%) of phthalic thioanhydride (**32**), mmp 110°.

The methylene chloride insoluble product gave 0.2 g of a yellow solid, mp 324–325°. Our attempts to purify this sample by recrystallization from common organic solvents were unsuccessful, in view of its very low solubility.

Anal. Calcd for $C_{16}H_8O_3S$: C, 68.57; H, 2.86. Calcd for $C_{16}H_8O_2S_2$; C, 64.86; H, 2.70. Found: C, 68.69; H, 2.79.

The ir spectrum (KBr) of the yellow mixture showed absorption bands at 1786 (γ-lactone C=O), 1695 (γ-thiolactone C=O), 1736 (δ-lactone C=O), and 1647 cm^{-1} (δ-thiolactone C=O).

The uv spectrum (CH_2Cl_2) was characterized by the following absorption maxima: 384 nm (ε 13,000), 372 (13,800), 306 (4830), 284 (4560), 270 (6100).

The mass spectrum of the yellow mixture showed prominent peaks at *m/e* 296, 280, 264, 252, 240, 236, 232, 224, 208, 195, 196, 180, 163, 153, 120, 104, 76, and 50.

Treatment of the yellow product with boiling methylene chloride could bring a small quantity of it in solution and testing this dilute solution on a tlc plate revealed the presence of at least three components. The top spot on the tlc plate showed no fluorescence under a uv lamp, whereas the middle spot and the bottom spot showed blue and green fluorescence, respectively. Employing preparative tlc, we have been able to separate the components from a small quantity of the mixture.

Extraction of the top spot on the tlc plate with methylene chloride gave a light yellow solid, mp 350°, which showed no depression in its melting point with an authentic sample of **37**.[10]

The ir spectrum (KBr) of **37** showed an absorption band at 1700 cm^{-1} due to the C=O group in a γ-thiolactone[10] and was identical with that of an authentic sample.

The uv spectrum (CH_2Cl_2) of **37** was characterized by the following absorption maxima: 292 nm (ε 4740), 304 (5200), 316 (4750), and 400 (19,750).

Extraction of the middle spot on the tlc plate with methylene chloride gave a yellow solid, mp 339–340°, which showed no depression in its melting point when mixed with an authentic sample of 2-thio-3,3′-biphthalide (**35**).[10]

The ir spectrum (KBr) of **35** showed two absorption bands at 1792 and 1704 cm^{-1} due to the C=O groups in γ-lactone and γ-thiolactone, respectively. The ir spectrum was superimposable on that of an authentic sample of **35**.

The uv spectrum (CH_2Cl_2) of **35** was characterized by the following absorption maxima: 274 nm (ε 5700), 300 (6550), 314 (6700), 380 (21,850) and 392 (20,850).

Extraction of the bottom spot on the tlc plate with methylene chloride gave a pale yellow solid, mp 340°, which showed no depression in its melting point when mixed with an authentic sample of **36**.[10]

The ir spectrum (KBr) of **36** showed two absorption bands at 1754 and 1667 cm^{-1} due to the C=O groups in δ-lactone and δ-thiolactone, respectively. The ir spectrum of **36** was identical with that of an authentic sample.

The uv spectrum (CH_2Cl_2) of **36** was characterized by the following absorption maxima: 272 nm (ε 42,000) (shoulder), 284 (26,900), 308 (32,750) (shoulder), 320 (48,700), 356 (54,600), 370 (66,350), and 386 (50,400).

Further confirmation of the structure of **36** was derived from its mass spectrum, which showed the molecular ion peak at *m/e* 280.

The pyrolysis of **5b** under similar conditions gave a 24% yield of carbonyl sulfide, identified through its piperidinium salt (mp 112°), 16% of phthalic thioanhydride, mmp 110°, and 9% yield of the mixture consisting of **35**, **36**, and **37**, as identified on a tlc plate. Similarly, the thermal decomposition of **5c** gave a 30% yield of carbonyl sulfide, a 25% yield of phthalic thioanhydride, and a 15% yield of the mixture consisting of **35**, **36**, and **37**.

Reaction of 3-Chloro-3-phenylphthalide (6) with Potassium *O*-Ethyl Xanthate (2a).—To an acetone solution (20 ml) of **6** (2.5 g, 0.1 mol) maintained around 5° was added 1.6 g (0.01 mol) of **2a**, in small portions and with stirring, over a period of 30 min. Removal of the solvent under vacuum gave a product which was treated with water to remove any unchanged **2a** and was recrystallized from a mixture (1:1) of methylene chloride and methanol to give 2.1 g (60%) of *O*-ethyl *S*-(3-phenylphthalidyl) xanthate (**9**), mp 88°.

Anal. Calcd for $C_{17}H_{14}O_3S_2$: C, 61.81; H, 4.24. Found: C, 61.89, H, 4.27.

The ir spectrum (KBr) of **9** showed an absorption band at 1786 cm^{-1} due to the C=O group (γ-lactone).

The uv spectrum (CH_2Cl_2) of **9** was characterized by the following absorption maxima: 284 nm (ε 17,050) and 366 (50).

The nmr spectrum ($CDCl_3$) of **9** showed a multiplet centered around δ 7.5 (9 H) due to the aromatic protons, a quartet at δ 4.17 (2 H) due to the methylene protons, and a triplet at δ 0.9 (3 H) due to the methyl protons.

Photolysis of *O*-Ethyl 3-(Phenylphthalidyl) Xanthate (9).—A solution of 0.5 g (0.0015 mol) of **9** in benzene (200 ml) was irradiated at room temperature for 30 min. Removal of the solvent under vacuum gave a product which on recrystallization from a mixture (1:1) of methylene chloride and ethanol gave 0.15 g (50%) of 3,3′-diphenylbiphthalide (**23**), mp 285–286° (lit.[8] mp 293°).

Anal. Calcd for $C_{28}H_{18}O_4$: C, 80.38; H, 4.30. Found: C, 80.24; H, 4.14.

The ir spectrum (KBr) of **23** showed a single C=O absorption at 1783 cm^{-1}, due to a γ-lactone grouping.

The uv spectrum (CH_2Cl_2) of **23** showed the following absorption maxima: 280 nm (ε 3550) and 288 (3820).

Thermal Decomposition of *O*-Ethyl 3-(Phenylphthalidyl) Xanthate (9).—Heating 0.66 g (0.002 mol) of the xanthate **9** at *ca.* 200° for 20 min and work-up of the pyrolyzed residue by treatment with ethanol in the usual manner gave 0.32 g (76%) of **23**, mmp 285–286°.

Reaction of 3-Chlorophthalide (1) or 3-Bromophthalide (10) with Dithiocarbamates (11a–e).—In a representative run, 0.01 mol of **11a** was added to a solution of **1** in acetone (0.01 mol in 25 ml), maintained around 5°, over a period of 30 min. Removal of the solvent under vacuum gave a product which was

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TABLE I

3-[(DIALKYLTHIOCARBAMOYL)THIO]PHTHALIDES

Compd	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Ir, cm^{-1} (KBr), C=O (γ-lactone)	Uv, λ_{max}, nm (ε)
14a	62,[a] 86[b]	186–187	50.00	4.54	5.78	50.27	4.53	5.56	1750	282 (11,850), 340 (90)
14b	85[b]	121–122	55.51	5.33	4.96	55.30	5.28	5.25	1760	284 (11,350), 340 (120)
14c	64,[a] 64	175–176	55.91	4.65	5.0	56.16	4.60	5.09	1750	284 (13,100), 334 (100)
14d	75[b]	115–116	57.33	5.11	4.77	57.54	5.41	4.58	1760	286 (16,650), 340 (100)
14e	78[b]	167–168	52.88	4.40	4.74	52.65	4.23	4.67	1750	288 (14,800), 350 (130)

[a] In the reaction of **1** with dithiocarbamates. [b] In the reaction of **10** with dithiocarbamates.

TABLE II

3-PHENYLPHTHALIDYL DIALKYLDITHIOCARBAMATES

Compd	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Ir, cm^{-1} (KBr), C=O (γ-lactone)	Uv, λ_{max}, nm (ε)
19a	60	135–136	62.00	4.55	4.25	61.82	4.84	4.00	1770	286 (10,100), 360 (70)
19b	71	135–136	63.86	5.32	3.92	64.17	5.30	3.85	1773	290 (7,650), 364 (60)
19c	57	149–150	64.22	4.78	3.94	64.33	4.64	3.88	1776	290 (11,550), 366 (70)
19d	70	135–136	65.04	5.14	3.79	65.06	5.13	4.10	1770	290 (11,100), 366 (90)

washed with excess of water to remove any unchanged **11a** and recrystallized from a mixture (1:1) of ethanol and methylene chloride. Table I summarizes the percentage yields and the physical data of the different 3-[(dialkylthiocarbamoyl)thio]-phthalides (**14a–e**).

Photolysis of 3-[(Dialkylthiocarbamoyl)thio]phthalides (14a–e).—In a typical run, a solution of 1 g (0.004 mol) of **14a** in benzene (200 ml) was irradiated for 1 hr at room temperature. Removal of the solvent under vacuum gave a product which on recrystallization from acetic acid gave 0.11 g (27%) of *meso*-3,3′-dihydrobiphthalide (**21**), mmp 270°.

Under identical conditions, the photolysis of **14b** gave a 40% yield of **21**, whereas the photolysis of **14c**, **14d**, and **14e** gave 25, 27, and 25% yields of **21**, respectively.

Thermal Decomposition of 3-[(Dialkylthiocarbamoyl)thio]-phthalides (14a–e).—In a typical run, 0.25 g (0.001 mol) of **14a** was heated at *ca.* 230–240°, under a nitrogen atmosphere, for 20 min. The evolved gases were passed into a 10% solution of piperidine in diethyl ether. No piperidinium salt of either COS or CS_2 precipitated out. Work-up of the pyrolyzed residue as in the case of *O*-alkyl *S*-phthalidyl xanthates resulted in the isolation of 0.018 g (12%) of a mixture of **35**, **36**, and **37**, melting over the range 324–325°, as identified by tlc comparison.

Under identical conditions, the thermolysis of **14b** (14%), **14c** (15%), **14d** (14%), and **14e** (17%) gave, in each case a mixture of products consisting of **35**, **36**, and **37**, in yields indicated in parentheses.

Reaction of 3-Chloro-3-Phenylphthalide (6) with Dithiocarbamates (11a–d).—In a representative run, 0.01 mol of **11a** was added to an acetone solution of **6** (0.01 mol, 20 ml), maintained around 5°, for a period of 45 min. Removal of the solvent under vacuum gave a product which was washed with excess of water to remove any unreacted **11a** and recrystallized from a mixture (1:1) of ethanol and methylene chloride. Table II summarizes the physical data of the different 3-phenylphthalidyl dialkyldithiocarbamates (**19a–d**).

Photolysis of 3-Phenylphthalidyl Dialkyldithiocarbamates (19a–d).—In a typical run, a solution of 0.66 g (0.002 mol) of **19a** in benzene (175 ml) was irradiated for 1 hr at room temperature. Removal of the solvent under vacuum and work-up of the mixture in the usual manner gave 0.21 g (50%) of 3,3′-diphenylbiphthalide (**23**), mmp 285–286°, after recrystallization from a mixture (1:1) of ethanol and methylene chloride.

In similar experiments, the photolysis of **19b**, **19c**, and **19d** gave **23** in 57, 57, and 45% yields, respectively.

Thermal Decomposition of 3-Phenylphthalidyl Dialkyldithiocarbamates (19a–d).—In a typical run, 0.33 g (0.001 mol) of **19a** was heated at *ca.* 200° under nitrogen atmosphere for 20 min. The pyrolyzed residue was treated with a small quantity of ethanol to give 0.15 g (72%) of 3,3′-diphenylbiphthalide (**23**) mmp 285–286° on recrystallization from a mixture (1:1) of ethanol and methylene chloride.

Under similar conditions, the thermal decomposition of **19b** (80%), **19c** (70%), and **19d** (60%) gave **23** in each case, in yields indicated in parentheses.

Registry No.—**5a**, 32819-73-1; **5b**, 32819-74-2; **5c**, 32819-75-3; **9**, 32785-00-5; **14a**, 32819-76-4; **14b**, 32958-89-7; **14c**, 32819-77-5; **14d**, 32851-12-0; **14e**, 32819-78-6; **19a**, 32785-01-6; **19b**, 32819-79-7; **19c**, 32785-02-7; **19d**, 32819-80-0; **21**, 4281-21-4; **35**, 32819-82-2; **36**, 23667-34-7; **37**, 32819-84-4.

Nucleophilic Reactivity to Diphenylcarbamoyl Derivatives. The Unimolecular Nature of Diphenylcarbamoyl Chloride Hydrolysis

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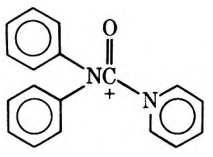
The nucleophilic reactivity of the fluoride, chloride, imidazole, pyridine, and *p*-nitrophenyl diphenylcarbamoyl derivatives have been investigated. The pyridinium ion is reactive to nucleophiles, following closely the reactivity sequence of these nucleophiles to *p*-nitrophenyl acetate. On the other hand, except for amine nucleophiles, diphenylcarbamoyl chloride is insensitive to nucleophiles, reacting instead with water. The $\Delta S^{\pm}$ of -5 eu for the water reaction and the small deuterium solvent isotope effect of 1.2 strongly suggest that diphenylcarbamoyl chloride hydrolyzes by an ionization reaction.

Diphenylcarbamoyl chloride (**1**) is known to specifically inactivate chymotrypsin[3,4] and cholinesterase.[5] This fact is very interesting because carbamoyl chlorides are thought to undergo hydrolysis by an ionization mechanism[6] and therefore to be insensitive to nucleophilic attack. If this is so, then the enzyme must be able to alter the mechanism of displacement reactions with the acid chloride, so that the ionization mechanism is bypassed by a lower energy process of direct reaction with the enzyme. For this reason we have studied in detail the sensitivity of the acid chloride and of the pyridinium derivative to nucleophilic attack. Diphenylcarbamoylpyridinium ion (**2**) has been found to be a good irreversible inhibitor of a variety of serine esterases and proteinases as well as of urease.[7]

1



2

Results

Diphenylcarbamoyl Chloride.—**1** has no reactivity to acetate, sulfite, phosphate, or formate, as demonstrated by the identical rate constants obtained in the presence or absence of these agents (Table II). No acid-catalyzed hydrolysis is observed in 1 *M* HCl or $HClO_4$. Concentrations of phosphate or acetate as high as 0.9 or 1 *M* give rise to quantitative yields of diphenylamine with identical rates. Had diphenylcarbamoyl phosphate been produced, then diphenylamine would not be produced in quantitative yield, because separate experiments with diphenylcarbamoylpyridinium ion, which reacts rapidly with phosphate to produce the phosphate derivative with a λ_{max} at 248 nm, demonstrate that the intermediate yields diphenylamine only slowly over the period of a week.

On the other hand, diphenylcarbamoyl chloride reacts readily with amine-containing buffers. In the case of imidazole the diphenylcarbamoylimidazole product, λ_{max} 233 nm, can be spectrophotometrically detected as well as the diphenylamine (λ_{max} 280 nm) product. In addition diphenylcarbamoylimidazole can be isolated from aqueous solutions containing imidazole and **1**. (See Experimental Section.) The yield of the diphenylamine decreases as the yield of diphenylcarbamoylimidazole increases and the total rate increases with the increasing imidazole concentration in the buffer. These results are displayed in Table I. Similar product results are obtained in glycine containing buffers, 0.4 *M* in Tris, pH 8.3, in which the glycine concentration varies from 0.1×10^{-3} to 5×10^{-3} to 10×10^{-3} *M*. The yield of diphenylamine determined at 280 nm decreases in this series from 100 to 67 to 29%. These results are in accord with eq 1, which describes

TABLE I

YIELD OF DIPHENYLAMINE FROM DIPHENYLCARBAMOYL CHLORIDE IN IMIDAZOLE BUFFERS[a]

Buffer composition	Yield, % diphenylamine	Calcd,[b] % diphenylamine
0.05 *M* Im, 0.05 *M* ImH	52	48
0.10 *M* Im, 0.02 *M* ImH	36	31
0.15 *M* Im, 0.03 *M* ImH	22	23
0.10 *M* Im, 0.01 *M* ImH	46	31
0.20 *M* Im, 0.02 *M* ImH	24	18

[a] Constant ionic strength of 0.20 *M* maintained with KCl. Temperature is 25°. [b] Calculated from eq 1 substituting imidazole for glycine and using 0.0020 min^{-1} for k_b and 0.045 M^{-1} min^{-1} for k_g.

$$100/\%\ \text{diphenylamine} = 1 + k_g(\text{glycine})/k_b \qquad (1)$$

the expected yield of diphenylamine in terms of the kinetic constant observed in a separate set of experiments. Diphenylcarbamoyl chloride is known to react with amino acids, including glycine, in water–ethanol mixtures to give high yields of crystalline diphenylcarbamoyl derivatives.[8] In eq 1 k_g is the apparent catalytic coefficient of glycine in the buffer, and k_b is the constant buffer term. The derivation of eq 1 was made assuming that competitive kinetics[9a] give rise to diphenylamine as the hydrolysis product and diphenylcarbamoylglycine as the product of nucleophilic attack by glycine. The latter urea derivative is assumed to be optically transparent at 280 nm in analogy with 1,1-diphenylurea, which has a λ_{max} at 235 nm. A plot of eq 1 yields a straight line with a value of 50 M^{-1} for

(1) This work was supported by Grant GM-11834 from the U. S. Public Health Service.

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TABLE II
KINETICS OF DIPHENYLCARBAMOYL CHLORIDE IN AQUEOUS SOLUTIONS[c] AT 25°

Reactant solution[b]	μ, M[a]	pH	k_o, min^{-1}	k_n, M^{-1} min^{-1}
0.20 M $HClO_4$	0.20–1.0[i]		0.00226 ± 0.00011	
1.0 M HCl	1.0		0.0017	
0–0.20 M $HClO_4$[g]	0.20		0.00225 ± 0.00015	
0–0.20 M HCl[h]	0.20		0.00193 ± 0.00020	k_{H_2O}/k_{D_2O} = 1.17
0–0.2 M DCl[j]	0.20		0.00165 ± 0.00011	
0.01 M HCl at 25°	0.01		0.00182	
0.01 M HCl at 48.8°	0.01		0.0308	
10% MeCN	0		0.0015	
1.0 M KCl, 10% MeCN	1.0		0.00148	
2.45 M KCl, 10% MeCN	2.45		0.00109	
0.20 M Na formate, 0.20 M formic acid, and five dilutions	0.20	3.81	0.0020	<0.002
0.20 M NaOAc, 0.10 M HOAc, and five dilutions	0.20	4.78	0.0018	<0.002
1.0 M NaOAc, 0.08 M HOAc in 10% MeCN	1.0	5.58	0.0014	<0.0002
0.05 M Na_2HPO_4, 0.05 M NaH_2PO_4, and five dilutions	0.20	6.85	0.0017	<0.007
0.90 M Na_2HPO_4, 0.10 M NaH_2PO_4, 0.10 M NaCl in 10% MeCN	2.45	7.51	0.0005	<0.0001
Hydrazine, 10^{-4}, 10^{-3}, 5×10^{-3}, 10^{-2} M in 0.2 M K_2CO_3 buffer	0.20	10.3	0.0018	0.70
Hydroxylamine, 10^{-4}, 10^{-3}, 5×10^{-3}, 10^{-2} M in 0.2 M K_2CO_3 buffer	0.20	10.3	0.0016	0.24
Hydroxylamine, 10^{-4}, 10^{-3}, 5×10^{-3}, 10^{-2} M in 0.4 M Tris buffer	0.20	8.4	0.0025	0.26
0.2 M Na_2SO_3	0.60	9.71	0.0014	<0.001
0.2 M NaN_3	0.20	9.5		0.063
Butylamine, 10^{-4}, 5×10^{-4}, 10^{-3} M in 0.2 M K_2CO_3 buffer	0.20	10.3		0.55[f]
Glycine, 10^{-4}, 5×10^{-4}, 10^{-3}, 5×10^{-2}, 10^{-1} M in 0.40 M Tris buffer	0.20	8.4	0.0025	0.14[e]
Glycine, 10^{-3}, 5×10^{-3}, 10^{-2}, 10^{-1} M in 0.2 M K_2CO_3 buffer	0.20	10.4	0.0015	0.18[e]
0.18 M Im, 0.18 M ImH, and five dilutions	0.20	7.45	0.0020	0.036
0.08 M Im, 0.008 M ImH, and four dilutions	0.20	8.08	0.0022	0.052
0.70 M Im, 0.10 M ImH, and five dilutions	0.20	7.83	0.0020	0.052
0.20 M Im, 0.04 M ImH, and five dilutions	0.20	7.90	0.0016	0.048
1.0 M Imidazole		10.1		0.049
0.60 M MeIm, 0.20 M MeImH, and one dilution	0.20	7.4	0.003	0.022
0.20 M Tris, 0.20 M TrisH	0.20	8.29	0.0018	<0.0018
0.20 M KF	0.20		0.0021	<0.001
$NaNO_2$, 10^{-3}, 10^{-2}, 5×10^{-2} M in 0.2 M K_2CO_3 buffer		10.3	0.0022	0.008
Mercaptoethanol, 0.063 and 0.016 M in 0.1 M phosphate buffer, 10% MeCN	0.20	7.78	0.015	<10[d]
0.90 M pyridine, 0.09 M pyridineH in 10% MeCN	0.09	6.2		0.045
NaOH, 0.01, 0.04, 0.06, 0.08, 0.10, 0.14, 0.20 M	0.20		0.0019	1.04

[a] Ionic strength maintained with KCl unless otherwise noted. [b] Abbreviations used: Im, imidazole; MeIm, *N*-methylimidazole; HOAc, acetic acid; MeCN, acetonitrile; Tris, tris(hydroxyethyl)aminomethane. [c] Concentration of diphenylcarbamoyl chloride is 4×10^{-5} M. The substrate was dissolved in acetonitrile and introduced into the reaction medium to initiate the reaction. The final concentration of acetonitrile is 0.3% unless otherwise noted. k_o refers to the water term and k_n refers to the second order nucleophile term. [d] Calculated using a value of 9.5 for the pK_a of mercaptoethanol. [e] Calculated using a value of 9.6 for the pK_a of glycine. [f] Calculated using a value of 10.6 for the pK_a of butylamine. [g] Five separate determinations. [h] Nine separate determinations. [i] Five separate determinations in $NaClO_4$–$HClO_4$ mixtures. [j] Three separate determinations in 0.05, 0.10, and 0.20 M DCl, μ = 0.20.

k_g/k_b, the slope. This is in good agreement with the value of 0.071 M^{-1} min^{-1}/0.0025 min^{-1} = 28 M^{-1} obtained in the separate kinetic experiments.

The kinetics of the disappearance of **1** in various buffers are given in Table II. The salt effects and cosolvent effects are fairly small, as demonstrated by the less than 10% rate effect in the perchloric acid buffers of ionic strength varying from 0.02 to 1.0 M and the

TABLE III

KINETICS OF DIPHENYLCARBAMOYLPYRIDINIUM ION IN AQUEOUS SOLUTIONS AT 25°[e]

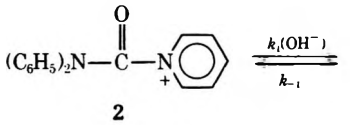
Reactant solutions	pH	k_{obsd}, min^{-1}	k_2, M^{-1} min^{-1}
H_2O–10^{-3} M HCl[a]		4.95×10^{-4}	
OH^-, determined[b] in 0.12 M Na_2CO_3 buffer and four dilutions	9.75	1.40 ± 0.25	$0.25 \pm 0.05 \times 10^5$
OH^-, determined[b] in 0.20 M Na_2CO_3 buffer and three dilutions	9.43	2.2 ± 0.2	$0.8 \pm 0.08 \times 10^5$
1.0 M NaOAc, 0.10 M HOAc[c]	5.68	0.17, 0.18	0.17, 0.18
0.50 M NaOAc, 0.05 M HOAc	5.65	0.079	0.16
1.0 M Na formate, 0.10 M formic acid[c]	4.58	0.18	0.18
1.0 M Na formate, 0.10 M formic acid[a]	4.58	0.21, 0.18	0.21, 0.18
0.50 M Na formate, 0.05 M formic acid[a]	4.55	0.13	0.26
0.02 M Sodium phosphate buffer[d]	7.0	0.0167, 0.0168	1.2
0.10 M Sodium phosphate buffer	7.56	0.069	0.78
0.02 M Tris buffer	7.28	0.0038	2.0
0.02 M Tris buffer[d]	9.0	1.16	3.6
Mercaptoethanol 0.0135 M in 0.02 M phosphate buffer[d]	7.0	20	4.7×10^5 [d]
Mercaptoethanol, 0.0068 M in 0.2 M phosphate buffer[d]	7.0	11	5.2×10^5
Mercaptoethanol, 0.000138 M in 0.02 M phosphate buffer[d]	7.0	0.20, 0.26	5.6×10^5, 4.2×10^6

[a] Followed at 280 nm. [b] Followed at 340 nm. [c] Followed by alkaline quenching method. [d] Based on a pK_a value of 9.5 for mercaptoethanol. [e] Abbreviations: Tris, tris(hydroxymethyl)aminomethane; AcO, acetate.

25% rate decrease obtained by adding 10% acetonitrile to the aqueous medium. The reaction of **1** with hydroxide is relatively slow, with the result that the alkaline hydrolysis term does not become important until the pH is raised to 12.2. The activation parameters for the hydrolysis of **1** determined in 0.01 M HCl at 48.8 and 25° are $\Delta H^{\ddagger} = 22$ kcal and $\Delta S^{\ddagger} = -5$ eu. Diphenylcarbamoyl chloride hydrolyzes at nearly the same rate in heavy water as in light water, giving a value of 1.2 for the solvent deuterium isotope effect, k_{H_2O}/k_{D_2O}.

No terms second order in imidazole or first order in imidazole and first order in hydroxide ion could be detected for the interaction of diphenylcarbamoyl chloride with imidazole, when the reaction is carried out in a 1.0 M imidazole solution at pH 10.9.

Diphenylcarbamoylpyridinium Chloride.—In contrast to **1**, **2** is very sensitive to attack by nucleophiles, as demonstrated by the kinetic results in Table III. Also, **2** undergoes a ring-opening reaction in more alkaline solution to produce the Schiff base of 1,1-diphenylurea and glutacondialdehyde **3**, which absorbs maximally at 422 nm in its anionic form and 340 nm in its neutral form, $pK_a = 12$ according to eq 2. This



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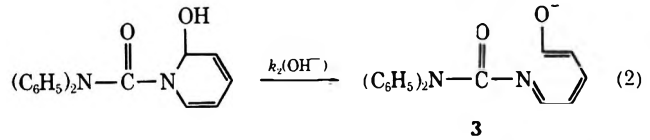


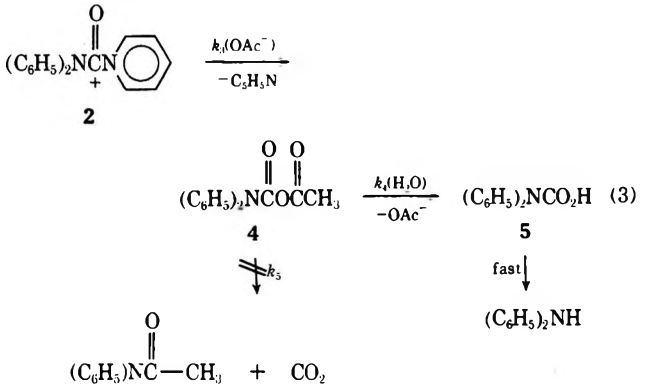
(2)

3

reaction is second order in hydroxide with a specific rate constant of k_1k_2/k_{-1} of 10^9 M^{-2} min^{-1}, as determined by using the same techniques as were used with dimethylcarbamoylpyridinium ion.[10]

(10) S. L. Johnson and K. A. Rumon, *Biochemistry*, **9**, 847 (1970).

The products of the reaction of nucleophiles with diphenylcarbamoylpyridinium ion have varying degrees of stability. The acetate derivative is only stable enough to be detected as a kinetic intermediate in the reaction given by eq 3. The intermediate diphenyl-



2

4 **5**

(3)

carbamoyl acetate **4** yields diphenylamine quantitatively in the k_4 step with a rate comparable to the rate of attack of 0.5 or 1.0 M acetate with **2** in the k_3 step. The kinetics of diphenylamine production followed at 280 nm are not first order, but rather show a lag period and therefore were treated by the method of consecutive kinetics. The rate constant for the interaction of acetate with **2** is 0.17 min^{-1} M^{-1}, as determined separately by the alkaline quenching method which measures directly the substrate concentration. The rate constant for the production of diphenylamine from **4** is estimated to be 0.25 min^{-1} when the absorbance changes at 280 nm are treated according to eq 4. A similar treatment

$$\frac{[(C_6H_5)_2NH]_t}{[(C_6H_5)_2NH]_0} = 1 + \frac{1}{k_3 - k_4}(k_4e^{-k_4t} - k_3e^{-k_3t}) \quad (4)$$

of the reaction in 0.5 M acetate buffer yields a nearly identical value of 0.20 min^{-1} for k_4, indicating that the intermediate **4** is not subject to nucleophilic or general base-catalyzed decomposition under these conditions. The decomposition rate of diphenylcarbamic acid **5**

under the conditions used here (pH 5.7) is much greater than the rate of formation of **5**, so that k_4 is rate limiting in the production of diphenylamine. The rate constant for this process is 10^2 min^{-1}.[11] The properties of diphenylcarbamoyl acetate can be compared with those of dimethylcarbamoyl acetate ($k_4 + k_5 > 0.08$ min^{-1}), which is produced from the reaction of dimethylcarbamoylpyridinium ion with acetate at a lower rate than its decomposition rate.[12] The acetate derivative yields 50% dimethylacetamide by rearrangement and 50% dimethylamine by hydrolysis at pH 5.4.[12] In contrast **4** does not internally rearrange (the k_5 step in eq 3), but rather quantitatively yields diphenylamine in the k_4 hydrolysis step.

The intermediate diphenylcarbamoyl formate, produced from the interaction of formate with **2**, decomposes with a rate constant which is at least five times greater than the rate constant for its production in the presence of 0.5 and 1.0 M formate. This is demonstrated by the identical first-order kinetics obtained from measuring either the amount of substrate present by the method of alkaline quenching, or by measuring the amount of diphenylamine produced by observing the reaction at 280 nm. A quantitative yield of diphenylamine was obtained, indicating that the intermediate diphenylcarbamoyl formate hydrolyzes only to diphenylamine rather than internally rearranging to diphenylformamide, which would be expected if its behavior were similar to that of dimethylcarbamoyl formate.[12]

The reaction of **2** with mercaptoethanol yields a stable thiol ester of diphenylcarbamic acid which absorbs maximally at 241 nm and does not hydrolyze to diphenylamine at pH 7.0 in a 0.1 M phosphate buffer over a period of 1 week. That **2** reacts with thiol to yield thiol esters, rather than other products such as pyridine ring addition products, is demonstrated by the isolation in high yield of the mercaptoethanol thiol ester upon treatment of **2** with mercaptoethanol in aqueous solution. (See Experimental Section.) The phosphate derivative of **2** absorbs maximally at 237 nm and decomposes very slowly at pH 7.56 to diphenylamine with an estimated half-life of 3–4 days. The hydroxylamine derivative of **2** or of **1** is very rapidly formed in a 0.1 M hydroxylamine solution, pH 6.3, and absorbs maximally at 237 nm, slowly decomposing overnight to give nearly quantitative amounts of diphenylamine as determined spectrally at 280 nm. Sodium sulfite reacts exceedingly rapidly with **2** to form a highly absorbing intermediate, λ_{max} 276 nm, which slowly decomposes over a week's time to the lesser absorbing diphenylamine. The sulfite reaction is too fast to measure using conventional techniques at pH 7 when quantities of sulfite as low as 10^{-4} M are used. The azide derivative of **2** is quite stable at pH 7.3, decomposing exceedingly slowly over a period of 1 week to give only slightly increased absorption at 280 nm. The above products from the interaction of **2** with nucleophiles are assumed to be the diphenylcarbamylated products by analogy with the corresponding dimethylcarbamylation of nucleophiles by dimethylcarbamoyl pyridinium ion.[12] Also, we have prepared diphenylcarbamoyl fluoride by treatment of **2** with KF in 10% aqueous acetonitrile. (See Experimental Section.)

Diphenylcarbamoylimidazole.—Because of the possibility that enzyme inhibition could involve histidyl residues, the chemical properties of diphenylcarbamoylimidazole were investigated. This compound represents an exceedingly stable acylimidazole derivative. Its spectrophotometrically determined pK_a value is 3.5. The rate of diphenylamine production followed in a 0.55 M formate buffer at pH 2.36 and in a 0.60 M formate buffer at pH 2.72 gives rate constants of 1.12×10^{-5} and 1.58×10^{-5} min^{-1} at 26°, respectively. These results can be analyzed according to eq 5. In contrast to its unreactivity to water and carboxylate ion, a rapid reaction of diphenylcarbamoylimidazole is observed with hydroxide ion, the specific rate constant from which is 3.6 M^{-1} min^{-1}, determined in 0.01–1.0 M NaOH solutions at 25°. This value is three times greater than the corresponding value for diphenylcarbamoyl chloride.

$$\text{rate} = [5.6 \times 10^{-5} + (\text{formate})\,9.2 \times 10^{-5}] \times [(C_6H_5)_2NCOImH^+]\ min^{-1} \quad (5)$$

Other Diphenylcarbamoyl Derivatives.—The rate of the alkaline reaction of the *p*-nitrophenyl ester and of the alkaline and water reactions of the fluoride were determined. These results are summarized in Table IV with the alkaline and water reactions of the chloride, imidazole, and pyridinium derivatives.

TABLE IV

RATE CONSTANTS FOR THE HYDROXIDE AND WATER REACTIONS OF DIPHENYLCARBAMOYL DERIVATIVES AT 25°

Derivative	k_w, min^{-1}	k_{OH}, M^{-1} min^{-1}
Fluoride	3.8×10^{-6} [a]	77[b]
Chloride	1.8×10^{-3}	1.04
p-Nitrophenol		0.018[c]
Pyridine	4.95×10^{-4}	$2.5–8.0 \times 10^5$
Imidazole		3.6

[a] Determined in 10^{-1}–10^{-3} M HCl, 10% acetonitrile. [b] Determined in 10^{-2} M NaOH. [c] Determined in 0.88 M NaOH.

Discussion

The sensitivity of diphenylcarbamoyl chloride to reaction with nucleophiles is very small. This lack of sensitivity is most apparent in the low value of k_{OH}/k_w, the ratio of the hydroxide rate constant and the water rate constant, 500 M^{-1} for this substrate. The fluoride, on the other hand, has a k_{OH}/k_w value of 2×10^8 M^{-1}. Typical values of k_{OH}/k_w for most esters, both reactive and unreactive, is 10^9–10^{10} M^{-1}. Examples are 1.7×10^9 M^{-1} for diphenylcarbamoylpyridinium ion found here, 7×10^9 M^{-1} for *p*-nitrophenyl acetate, 20×10^{10} M^{-1} for phenyl acetate, 3.6×10^9 M^{-1} for 1-acetoxy-4-methoxypyridinium perchlorate, 2.2×10^9 M^{-1} for acetyl-4-methylpyridinium ion, and 3.9×10^8 for methyl chloroacetate.[13–15] No reaction of anionic nucleophiles with diphenylcarbamoyl chloride could be detected in the case of carboxylates, sulfite, phosphate, and carbonate. The value of 678 M^{-1} min^{-1} for k_{OH}

(11) S. L. Johnson and D. L. Morrison, *J. Amer. Chem. Soc.*, **94**, 1323 (1972).
(12) S. L. Johnson and K. A. Rumon, *ibid.*, **87**, 4782 (1967).
(13) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **90**, 2622 (1968).
(14) A. R. Fersht and W. P. Jencks, *ibid.*, **92**, 5442 (1970).
(15) J. F. Kirsch and W. P. Jencks, *ibid.*, **86**, 837 (1964).

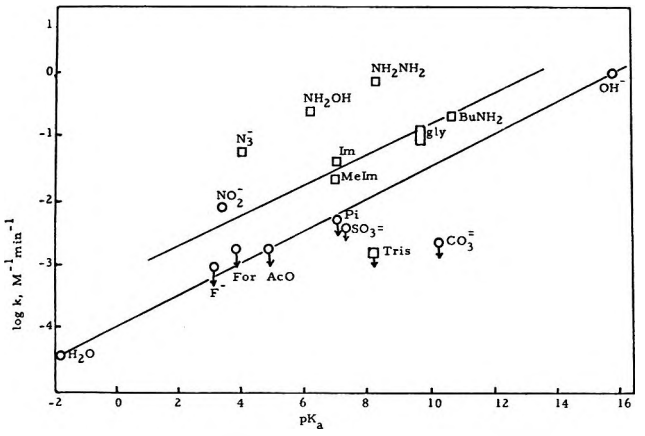


Figure 1.—Rate coefficients for nucleophilic reactions of diphenylcarbamoyl chloride *vs.* pK_a of the nucleophile. Abbreviations: gly, glycine; For, formate; AcO, acetate; Tris, tris(hydroxymethyl)aminomethane; Im, imidazole; MeIm, *N*-methylimidazole; Pi, phosphate; ○, oxygen nucleophiles; □, nitrogen nucleophiles. Data from Table II.

(32°, 25% acetonitrile) reported by Erlanger, *et al.*,[16] is in error, because this value was determined at a single pH value of 7.6 where there is no significant hydroxide reaction with diphenylcarbamoyl chloride. Because of the insensitivity to nucleophilic attack the hydroxide reaction does not become important until pH 11 due to its low value of 1 M^{-1} min^{-1}.

On the other hand, diphenylcarbamoyl chloride does react directly with amines forming the corresponding *N,N*-diphenylurea derivatives, and with the reactive anionic nucleophiles azide and nitrite. Greater reactivity to the "α effect" nucleophiles hydrazine and hydroxylamine than to primary amines of similar basicity is displayed, as shown in Figure 1, where the rate constants for the nucleophilic reactions are plotted against the pK_a of the nucleophile. The plot separates into two distinct lines; the amines are more reactive for their basicity than the oxygen nucleophiles water and hydroxide. The sensitivity to nucleophilic attack is small with the slope of the lines (the β values) being 0.25. The reactivity of nucleophiles to diphenylcarbamoyl chloride can be correlated with their nucleophilic reactivity to *p*-nitrophenyl acetate as shown in Figure 2 where also nucleophilic reactivity to diphenylcarbamoylpyridinium ion is shown. The slope for this plot is 0.5 for diphenylcarbamoyl chloride and 1.1 for diphenylcarbamoylpyridinium ion. The slope of 0.5 is considerably smaller than the slopes of unity for most reactions,[17] thereby suggesting very little bond making in the transition state for diphenylcarbamoyl chloride. The small negative entropy of activation of −5 eu and the solvent deuterium isotope effect of 1.2 for the water reaction of diphenylcarbamoyl chloride is in contrast to the large negative entropies of activation of −20 to −30 eu[18] and the sizable solvent isotope effects of >2 observed in the water reactions of most carboxylic acid derivatives.[17] These results, combined with the low sensitivity (low β) in nucleophilic displacement reactions, suggest that the transition state for the reaction

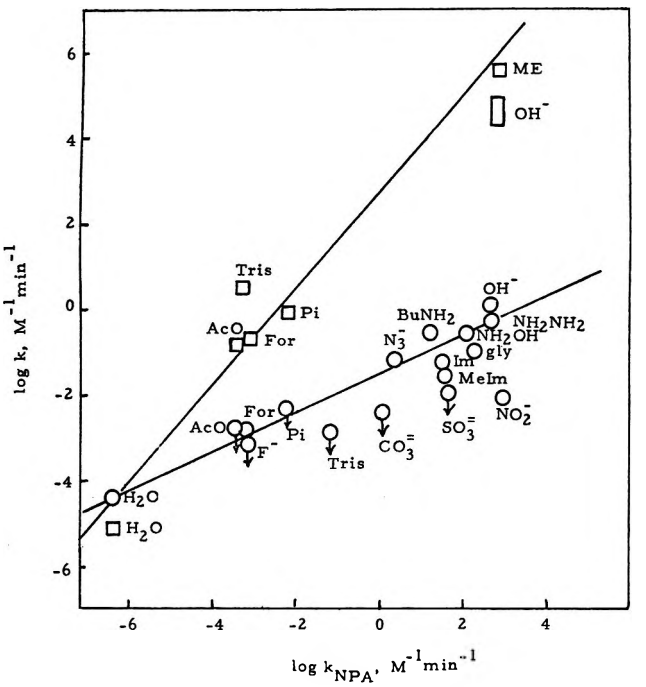
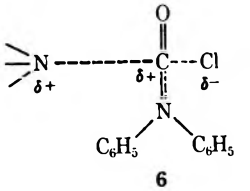


Figure 2.—Logarithmic plot of rate constants for the reactions of nucleophiles with *p*-nitrophenyl acetate, k_{NPA}, *vs.* the reactions of nucleophiles with diphenylcarbamoyl chloride, ○, and diphenylcarbamoylpyridinium ion, □. ME is mercaptoethanol; For, formate; AcO, acetate; Im, imidazole; MeIm, *N*-methylimidazole; Pi, phosphate. The formate rate constant for *p*-nitrophenyl acetate was estimated from the data of Fersht and Kirby[15a] for nucleophilic reactions of 2,4-dinitrophenyl acetate assuming a similar relative reactivity to *p*-nitrophenyl acetate. The other rate constants for *p*-nitrophenyl acetate has been summarized by Johnson.[17]

of diphenylcarbamoyl chloride with water and with other nucleophiles is very loose and nearly unimolecular. An even more extreme carbamoyl chloride reaction is that of dimethylcarbamoyl chloride, which exhibits an entropy of activation of 5 eu and is insensitive to reaction with added amine nucleophiles.[19,20]

In acyl transfer reactions from acyl compounds with good leaving groups Ferscht and Jencks found low sensitivity to the nucleophile basicity as well as low sensitivity to the basicity of the leaving group.[14] A very reactantlike transition state was suggested. The behavior of diphenylcarbamoyl chloride to nucleophilic reagents represents a very extreme example of low sensitivity to the reactivity of the nucleophile and can be accounted for by transition state **6**. The maintenance



6

of sensitivity to factors other than basicity in the reactivity of diphenylcarbamoyl chloride to the "α nucleophiles" hydrazine and hydroxylamine as well as to azide ion, a situation similar to the reactions of acylpyridinium ions, suggests that highly reactive nucleophiles do not require much bonding in transition state **6** to exert their special reactivity.[14]

(16) B. F. Erlanger, S. M. Vratsanos, N. H. Wasserman, and A. G. Cooper, *Biochem. J.*, **118**, 421 (1970).

(17) S. L. Johnson in "Advances in Physical Organic Chemistry," Vol. V, V. Gold, Ed., Academic Press, New York, N. Y., 1967.

(18) L. L. Schaleger and F. A. Long, "Advances in Physical Organic Chemistry," Vol. I, V. Gold, Ed., Academic Press, New York, N. Y., 1963, p 1.

(19) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **77**, 5993 (1955).

(20) I. Ugi and F. Beck, *Chem. Ber.*, **94**, 1839 (1961).

Experimental Section

Materials.—Diphenylcarbamoylimidazole was prepared by allowing 1 *M* imidazole to react with 0.025 *M* diphenylcarbamoyl chloride in 30% aqueous dioxane at room temperature for 24 hr. Crystals were collected and recrystallized from ethanol, mp 119.3–122.5°, $\nu_{C=O}$ 1695 cm^{-1}. Analysis was performed by Schwarzkopf Analytical Service, Woodside, N. Y. *Anal.* Calcd for $C_{15}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 72.90; H, 4.93; N, 15.68. Diphenylcarbamoyl chloride 1,1-diphenylurea, ethyl diphenylcarbamate, and diphenylamine are from Distillation Products Industries. *p*-Nitrophenyl diphenylcarbamate is from Sigma Chemical Co. Dimethylcarbamoylpyridinium chloride was prepared by the method of Johnson and Rumon.[21] Diphenylcarbamoylpyridinium chloride, mp 107.5–108.5°, was prepared by the method of Herzog.[22] Diphenylcarbamoyl fluoride, mp 81.8–82.0°, was prepared by allowing equimolar KF and diphenylcarbamoylpyridinium chloride to react in 10% acetonitrile, and twice recrystallized from ethanol. This product has the same melting point as the diphenylcarbamoyl fluoride obtained by treatment of diphenylcarbamoyl chloride with SbF_3 in xylene.[5] The mercaptoethanol thiol ester of diphenylcarbamic acid was prepared from the treatment of II, 0.10 *M*, with 0.2 *M* mercaptoethanol, pH 8.0, for 5 min. The product was isolated in 89% yield in the crude form and recrystallized from ethanol, mp 77.5–78.5°. Elemental analysis was performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. *Anal.* Calcd for $C_{15}H_{15}NO_2$: C, 65.91; H, 5.53; N, 5.13; S, 11.71. Found: C, 65.38; H, 5.59; N, 5.03; S, 13.23. The infrared spectrum of this compound (taken with a Beckman IR-4 spectrometer) shows an OH stretching frequency at 3450 cm^{-1}, a carbonyl stretching frequency at 1666 cm^{-1}, and a single carbonyl stretching frequency at 1666 cm^{-1}. The latter frequency is in contrast with the 1724 cm^{-1} frequency of ethyl diphenylcarbamate, and serves to rule out the formation of the isomeric oxygen ester in the reaction. The presence of the OH stretching frequency confirms this structure because the isomeric product would have only a weak band due to SH stretching at *ca.* 2400 cm^{-1}. The thiol ester product absorbs maximally at 241 nm in the uv.

Chemical Kinetics.—The hydrolysis rate of diphenylcarbamoyl chloride, fluoride, -imidazole, and -pyridinium ion was followed by measuring the increase in absorption produced at 280 nm by the diphenylamine product. In case of acetate, phosphate, Tris, and thiol-containing buffers which react directly with diphenylcarbamoylpyridinium to form products which do not rapidly liberate diphenylamine, the disappearance of the substrate was measured by utilizing the ability of carbamoylpyridinium ions to undergo ring-opening reactions which produce chromophoric materials.[20] In this case diphenylcarbamoylpyridinium ion is allowed to react with the desired buffer, and 1-ml aliquots are removed at timed intervals and placed in 5 0-ml portions of 1 *M* NaOH. The absorbances of these solutions are then measured at 422 nm. At this pH the chromophoric material disappears only slowly with a specific rate constant of 0.012 min^{-1}.

The reaction of diphenylcarbamoylpyridinium ion with more basic buffers was followed at 340 or 422 nm, which is a measure of the concurrent ring-opening process. The alkaline hydrolysis of diphenylcarbamoyl chloride was followed at 245 nm in 0.01–1 *M* NaOH. Diphenylcarbamate, λ_{max} 245 nm, is the stable product from this reaction from diphenylcarbamoyl chloride, λ_{max} 227 nm. The reaction of diphenylcarbamate to produce diphenylamine depends only on hydrogen ion and has a specific rate constant $k_H = 0.45 \times 10^8 M^{-1} min^{-1}$ at 25°.[11] The result is that this carbamate is the stable product of diphenylcarbamoyl chloride in alkaline solutions. The alkaline hydrolysis of diphenylcarbamoyl chloride and fluoride and of diphenylcarbamoylimidazole was also followed by a quenching procedure, in which appropriate amounts of 1 *M* acetic acid are added to aliquots from the alkaline reacting solutions. This gives a pH 4–6 solution, depending upon the conditions, in which diphenylcarbamate from the alkaline hydrolysis reaction readily produces diphenylamine which can be monitored at 280 nm. The pK_a of diphenylcarbamoylimidazole was measured by placing known quantities of the substrate in buffers of various pH values and measuring the absorbance of the acid form at 226.5 nm and the basic form of the substrate at 233 nm. The relationship $pK = pH + \log A_u - A/(A - A_i)$ was used, where A_i, A_u, and A are optical absorbances of the fully ionized form the unionized form, and observed form, respectively.

Analysis of Kinetics.—Semilog plots of $A_t - A_\infty$ *vs.* time were made, where the A's refer to the optical absorbances. Good linearity is achieved to past 90% reaction in most cases. The rate constant is calculated from the slope of the line divided by 2.303. The observed rate constants are plotted against the buffer concentration if a series of buffers of constant pH and varying concentration is used. The slope of such a plot is taken as the specific rate constant, k_2, for the interaction of the substrate with the buffer component. The intercept, k_1, is equal to $k_w + k_{OH^-}(OH^-)$, the sum of the water and hydroxide terms. In the case where hydroxide is the variable buffer component k_o refers to the water term, k_w.

Registry No.—**1**, 83-01-2; **2**, 33712-38-8; diphenylcarbamoyl fluoride, 10055-41-1; *p*-nitrophenyl diphenylcarbamate, 3848-46-2; diphenylcarbamoylimidazole, 2875-79-8; mercaptoethanol thiol ester of diphenylcarbamic acid, 33712-42-4.

Acknowledgment.—We wish to thank Mrs. Grace Tan and Mrs. Diana Kibby for carrying out some of the kinetic determination.

(21) S. L. Johnson and K. A. Rumon, *J. Phys. Chem.*, **68**, 3149 (1964).
(22) J. Herzog, *Ber.*, **40**, 1831 (1907).

Micellar Effects upon the Decarboxylation of 3-Bromo and 2-Cyano Carboxylate Ions[1]

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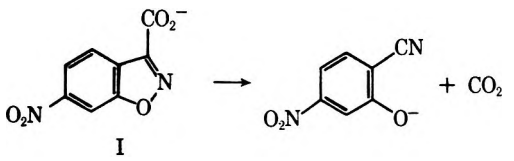
The decarboxylation of 2-cyano-2-phenylacetate ion *via* an intermediate carbanion is catalyzed *ca.* 660-fold by micelles of cetyltrimethylammonium bromide, CTABr, but that of 3-bromo-3-phenylpropionate ion *via* an intermediate carbonium ion is retarded by cationic micelles. The micellar-catalyzed decarboxylation of the 2-cyano acetate ion is enhanced by added inorganic salts, but added salts reduce the micellar inhibition of the decarboxylation of the 3-bromo propionate ion.

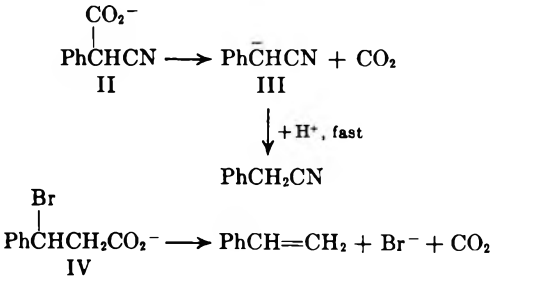
Decarboxylation of the 6-nitrobenzisoxazole-3-carboxylate ion (I) is strongly catalyzed by cationic micelles of cetyltrimethylammonium bromide (CTABr).[3] This implies that the transition state with its delocalized negative charge interacts more strongly than I with the cationic micelle. We were therefore interested in examining micellar effects upon decarboxylations of other carboxylate ions. Two reactions, having different mechanisms, were examined.

The decarboxylation of 2-cyanocarboxylate ions (II)

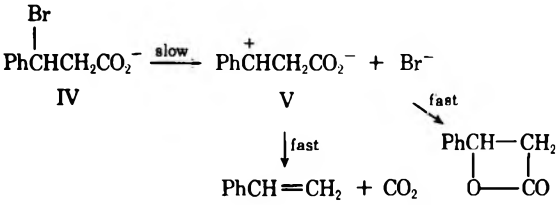
(1) Support of this work by the National Science Foundation and the Arthritis and Metabolic Diseases Institute at the U. S. PHS is gratefully acknowledged.
(2) U. S. PHS Postdoctoral Fellow.
(3) C. A. Bunton and M. J. Minch, *Tetrahedron Lett.*, 3881 (1970).



I



involves rate-limiting formation of a resonance-stabilized carbanion (III)[4] and, like the decarboxylation of benzisoxazole carboxylate ions,[5] is much faster in aprotic solvents than in water.[6] On the other hand, Bordwell and his coworkers have shown that the rate-limiting step of the decarboxylation of the 3-bromo-carboxylate ion (IV) is ionization to give a carbonium



ion (V) which either decarboxylates or collapses to a lactone.[8]

The solvolysis of similar 2-bromo carboxylate ions also proceeds *via* a carbonium ion.[8a] Such ionizations are not particularly sensitive to changes in the solvent, and the interaction between the carboxylate ion and the carbonium center appears to be electrostatic rather than covalent.

By analogy with other systems we expected that decarboxylation of II would be catalyzed by cationic micelles, but the situation should be more complex for the decarboxylation of IV. Incorporation of the 3-bromo carboxylate ion IV into a cationic micelle will stabilize the initial state and this of itself would reduce the reaction rate, but this inhibition may be offset by interaction between the cationic micelle and both the leaving bromide ion and the organic residue, especially if the latter is lactonelike.

There are many examples of electrolyte inhibition of micellar catalysis.[9,10] This inhibition appeared to be a general phenomenon and was readily explained in terms of competition between a counterion and the ionic reagent for the ionic micelle.[10,11] However, the rate of decarboxylation of I in the presence of micellized CTABr is increased by some salts,[12] and we were interested in finding other examples of this unexpected salt effect. The effectiveness of micelles as catalysts or inhibitors varies widely from one system to another and we are particularly interested in elucidating the factors which control these effects.

Experimental Section

Materials.—The 3-bromo-3-phenylpropionic acid was prepared by saturating a warm solution of cinnamic acid in acetic acid with HBr gas for 2.5 hr. The solvent was removed under reduced pressure on a rotary evaporator to yield the product which, after recrystallization from $CHCl_3$, had mp 139.5–141.5° (lit.[13] mp 137°).

Ethyl 2-cyanophenylacetate was prepared from benzyl cyanide[14] and was saponified by Hessler's method using 1 *M* NaOH.[15] After recrystallization from benzene, 2-cyano-2-phenylacetic acid had mp 69–72° (lit.[4] mp 72–73°). It appears that the compound can exist in more than one crystalline modification, because when the sample was kept at 50° for 3 days the melting point rose to 89–91°. On recrystallization from benzene the melting point went back to 69–72°.

The samples of CTABr and the dicationic surfactants (VI) were prepared and purified by methods already described.[11,16]

$$\text{cetyl}\overset{+}{\text{N}}\text{Me}_2(\text{CH}_2)_n\overset{+}{\text{N}}\text{Me}_2\text{cetyl}\ 2\text{Br}^-$$

VI

(a, b, c: n = 2, 4, 6, respectively)

Kinetics.—The reactions were followed spectrophotometrically using either a Cary 11 or a Gilford spectrophotometer with a water-jacketed cell compartment. The first-order rate constants, k_ψ, are in sec^{-1}.

The relatively rapid decarboxylation of 3-bromo-3-phenylpropionate ion (IV) was followed by introducing the acid, in 5 μl of ether, to 3 ml of aqueous surfactant containing 0.02 *M* NaOH in a cuvette. A perforated Teflon plunger was used to mix the solution rapidly in the cuvette. The substrate concentration was 5×10^{-5} *M*. The reaction was followed at 248 nm.

The decarboxylation of 2-cyano-2-phenylacetate ion (II) is relatively slow at room temperature.[4] An aqueous solution of the acid was added to a solution of CTABr and 1.7×10^{-2} *M* Tris buffer at pH 8; the resulting substrate concentration was $7\text{–}10 \times 10^{-4}$ *M*. The reaction was followed at 235 nm.

The change in absorbance is small for the decarboxylation of the 2-cyanocarboxylate ion (II), and the absorbance of CTABr compounds the problem; consequently, the rate constants have an uncertainty of *ca.* 10%. However, this accuracy is sufficient to establish the magnitude of the micellar catalysis.

Products of Decarboxylation of the 3-Bromo Acid (IV).—The formation of styrene and lactone from 3-bromo-3-phenylpropionate ion has been examined by Bordwell and Knipe.[8] If reaction took place in the micellar phase, the reaction products might change when the reaction mixture contains CTABr. In order to test this possibility we allowed a solution of 2×10^{-4} *M* IV to react at pH 8.1 in water and a second solution to react under the same conditions except that 10^{-2} *M* CTABr was present. After complete reaction, the first solution was also made 10^{-2} *M* in CTABr and it was found that the two mixtures had identical absorbances in the region 210–340 nm, so that there is no marked change of products in the two systems.

Spectral Measurements.—Because of their reactivity we could not examine II and IV in aqueous CTABr and therefore we measured the spectral shifts of the structurally similar 3-phenylpropionate ion, both in aqueous 0.05 *M* CTABr and in ethanol. In water 3-phenylpropionate ion has peaks at 267.2, 263, 257.5, 253.1, and 247.2 nm, the third and fourth peaks being the largest. The changes of wavelength and extinction coefficient of these peaks in CTABr and ethanol are given in Table I.

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(5) D. S. Kemp and K. Paul, *J. Amer. Chem. Soc.*, **92**, 2555 (1970).
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(9) E. J. Fendler and J. H. Fendler, *Advan. Phys. Org. Chem.*, **8**, 271 (1970).
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(15) J. C. Hessler, *Amer. Chem. J.*, **32**, 127 (1904).
(16) C. A. Bunton, L. Robinson, J. Schaak, and M. F. Stam, *J. Org. Chem.*, **36**, 2346 (1971).

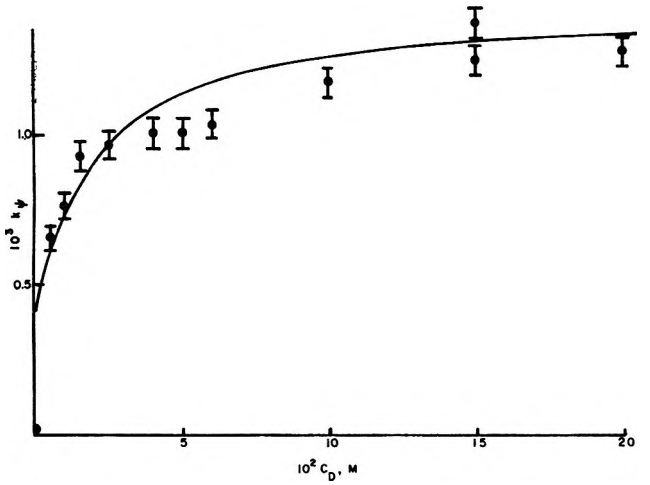

Figure 1.—Catalysis of the decarboxylation of 2-cyano-2-phenyl acetate ion by CTABr at 33.2°.

TABLE I
SPECTRAL SHIFTS OF 3-PHENYLPROPIONATE ION

Medium	Δλ, nm	Δε
0.05 *M* CTABr	+1.5	−25[a]
	+1.8	−7[b]
EtOH	+0.9	−32[a]
	+1.4	−14[b]

[a] Relative to ε 252 at 257.5 nm in water. [b] Relative to ε 248 at 260 nm in water.

These spectral shifts are consistent with incorporation of 3-phenylpropionate ion, and by analogy II and IV, in micellar CTABr (*cf.* ref 9).

Results

Kinetics.—Micelles of CTABr effectively catalyze the decarboxylation of 2-cyano-2-phenylacetate ion (Figure 1 and Table II), but they retard that of 3-bromo-3-phenylpropionate (Figure 2).

Micellar Catalysis.—The variation of k_ψ, for the decarboxylation of II, with CTABr concentration (c_D) shows the typical kinetic form of a spontaneous reaction catalyzed by micelles; that is, k_ψ increases to a plateau value, and then remains constant.[3,11,17] The kinetic forms characterized by a rate maximum rather than a plateau value are very common for bimolecular reactions catalyzed by micelles, suggesting that micellar deactivation of the external reagent is an important factor.[9,11] At lower temperatures the substrate is not soluble enough for accurate rate measurements in the absence of CTABr and the k_ψ values of 9.3×10^{-7} and 3.9×10^{-6} sec^{-1} for 25.0 and 33.2°, respectively, were calculated by extrapolation from $10^4 k_\psi = 1.42$ at 55.5°, 5.55 at 65.0°, and 10.8 at 69.8°. These rate constants gave a linear Arrhenius plot and Thomson's value of $10^4 k_\psi = 2.61$[4] at 60.0° fell on this plot. The activation parameters for reaction in the absence of surfactant are $\Delta H^\pm = 31.5$ kcal mol^{-1} and $\Delta S^\pm = 21$ eu, and are very similar to those for decarboxylation of the *p*-chloro compound.[4]

The activation parameters for decarboxylation catalyzed by 0.15 *M* CTABr are $\Delta H^\pm = 20$ kcal mol^{-1} and $\Delta S^\pm = -8.5$ eu (calculated from the rate constants in Figure 1 and Table II and $k_\psi = 30.6 \times 10^{-4}$ sec^{-1} at 39.9° in 0.15 *M* CTABr). The decrease of $\Delta H^\pm$ and $\Delta S^\pm$ for the micellar-catalyzed decarboxylation is similar to that observed by Cramer and Kampe for cyclodextrin-catalyzed decarboxylation,[7] and is readily explicable in terms of an incorporation of the substrate into the micelle. The maximum rate enhancements [*ca.* 660-fold at 25° and 360-fold at 33.2° based on plateau values of $k_\psi = 6.5 \times 10^{-4}$ sec^{-1} at 25.0° and 1.35×10^{-3} sec^{-1} at 33.2° (Figure 1 and Table II)] by micelles of CTABr are larger than that found for the decarboxylation of 6-nitrobenzisoxazole carboxylate ion.[3]

TABLE II
RATE CONSTANTS FOR THE DECARBOXYLATION OF 2-CYANOPHENYLACETATE ION IN CTABr[a]

$10^2 c_D$, *M*	$10^4 k_\psi$, sec^{-1}
0.0	0.0093
1.0	5.73
5.0	6.03
6.0	5.50
7.5	6.50
9.0	6.33
10.0	6.72
12.5	6.50
15.0	5.45

[a] At 25.0° at pH 8 (0.017 *M* Tris buffer).

TABLE III
SALT EFFECTS UPON THE DECARBOXYLATION OF 2-CYANOPHENYLACETATE ION IN CTABr[a]

	c_{salt}, *M*					
Salt	0.1	0.2	0.3	0.4	0.5	0.6
Na_2SO_4		1.84		2.22		2.44
NaCl	1.98	2.15		2.37		2.43
KCl	1.82	2.10	2.24			
KH_2PO_4	1.49		1.78	1.74	1.75	1.91
K_2HPO_4	1.70	1.75	1.88	2.17		

[a] Values of $10^3 k_\psi$, sec^{-1}, at 33.2° in 0.15 *M* CTABr; in the absence of added salt $10^3 k_\psi = 1.35$ sec^{-1}.

With some micellar-catalyzed or inhibited reactions it is possible to treat the kinetics in terms of an equilibrium binding of the substrate to the micelle and a rate constant for reaction in the micellar phase.[9,11,17,18] In order to use this approach the micellar concentration has to be greater than that of the substrate, so that a micelle will generally not contain more than one substrate molecule. This condition is not satisfied in our system because the small absorbance change in the reaction together with the absorbance of bromide ions forced us to use relatively high concentrations (*ca.* 10^{-3} *M*) of II.

As expected we find that the anionic surfactant sodium lauryl sulfate had no effect on the rate of decarboxylation of II because II should not be incorporated into an anionic micelle.

Salt Effects on the Micellar-Catalyzed Reaction.—Several added salts were found to increase the rate of decarboxylation of the 2-cyano acetate ion II in the presence of micellized CTABr (Table III). The effects are relatively small but are consistently greater than the experimental uncertainty. Although inorganic phosphate mono- and dianions have smaller effects than sulfate and chloride, the overall effects are not large

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TABLE IV
INHIBITION OF DECARBOXYLATION OF 3-BROMO-3-PHENYLPROPIONATE ION BY CATIONIC SURFACTANTS[a]

$10^4 c_D$, M	Surfactant VIa	VIb	VIc	CTABr
1.0		7.69	6.61	
2.0			2.40	
5.0		3.43		
10.0	5.0	2.83	1.47	14.0
20.0			1.27	10.0
100	2.44			
200	2.38			

[a] Values of $10^2 k_\psi$ at 25.0° in 0.02 M NaOH and 5×10^{-5} M substrate; in the absence of surfactant $10^2 k_\psi = 14.7$ sec^{-1}.

enough to show the marked salt specificity that was observed for the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion (I).[12] We were restricted in our choice of salts by the necessity of using only those which did not interfere with the rate measurements by absorbing strongly at 235 nm. We therefore could not use benzoate or tosylate ions which give a marked enhancement of the CTABr micelle-catalyzed decarboxylation of I at salt concentrations comparable to the CTABr concentration and retardation at higher salt concentrations.[12] The decarboxylation of I is catalyzed more by mixed micelles of CTABr and the nonionic detergent Igepal (an aryl polyether) than by micellized CTABr alone, suggesting that a decrease in the charge density of a cationic micelle assists the reaction,[3] but we could not use Igepal in the present work, because it absorbs too strongly at 235 nm. However, similarities between the decarboxylations of I and II suggest that both Igepal and the added salts assist decarboxylation by reducing the charge density of the cationic micelle.[3,12] These interactions between salts and micelles are being examined by nmr and electronic spectroscopy.

Micellar Inhibition.—The kinetic form of the inhibition of the 3-bromo-3-phenylpropionate ion (IV) is very simple (Figure 2). Qualitatively we would expect that there would be no inhibition below the critical micelle concentration (cmc) of CTABr, which is *ca.* 0.8×10^{-3} M.[9] (The cmc is affected by added solutes.) We observe a sharp rate decrease at CTABr concentrations above 1×10^{-3} M, in accord with this simple theory.

It is generally found that inhibiting micelles act by removing the substrate from the aqueous phase, in which it is reactive, into the micellar pseudophase, in which it is less reactive. On this hypothesis the steepness of the plot of k_ψ against c_D should be related to the strength of micelle–substrate binding. This expectation is fulfilled in the present system, where the 3-bromo-3-phenylpropionate ion (IV) should interact strongly with micellar CTABr. Shifts in the uv spectra of 3-phenylpropionate ion in CTABr micelles (Table I) are evidence for such interactions between carboxylate ions and cationic micelles.

Dicationic ammonium salts VI form micelles which are effective catalysts of nucleophilic attack of hydroxide ion upon halonitrobenzenes and hydroxide and fluoride ion upon *p*-nitrophenyldiphenyl phosphate.[16] These micelles are catalytically effective at low surfactant concentration, and we find that they inhibit decarboxylation of IV in low concentration, as is shown in Table IV. The surfactant derived from the ethanediamine needed to be in higher concentration than the corresponding butane and hexane derivatives to be an effective inhibitor (*cf.* ref 16).

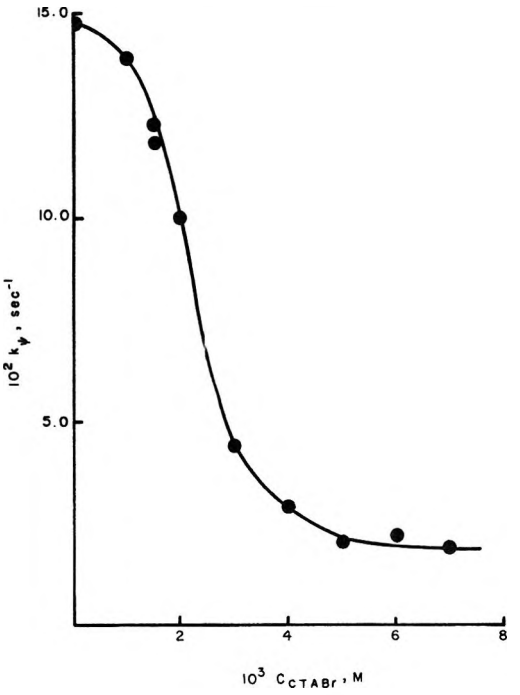

Figure 2.—Inhibition of the decomposition of 3-bromo-3-phenylpropionate ion by CTABr at 25.0°.

The values of k_ψ in the presence of relatively high concentrations of either CTABr or VI appear to level out at $k_\psi \approx 2 \times 10^{-2}$ sec^{-1}. At these surfactant concentrations, it can be assumed that the substrate will be wholly incorporated into the micellar pseudophase and that the reaction is therefore not stopped but merely slowed when the substrate is incorporated into a cationic micelle.

Added salts decrease the amount of inhibition by CTABr of the decarboxylation of 3-bromo-3-phenylpropionate ion (Table V). The salt effect is explicable in terms of the partial exclusion of the carboxylate ion IV from micelles of CTABr because of competition for sites on the micelle by added anions; sodium tosylate is especially effective in this role (*cf.* ref 12).

TABLE V
SALT EFFECTS UPON THE MICELLAR-INHIBITED REACTION OF 3-BROMO-3-PHENYLPROPIONATE ION[a]

c_{salt}, M	Salt NaCl	NaOAc	Na_2SO_4	NaTOS
0.01				7.86
0.20	4.50	2.45	3.20	
0.40	4.70	2.63	3.35	
0.60	5.01	3.30	3.30	

[a] Values of $10^2 k_\psi$, sec^{-1} at 25.0° in 0.02 M NaOH and 0.01 M CTABr. In the absence of added salt $10^2 k_\psi = 1.66$ sec^{-1}.

Discussion

Inhibition of Reactions of the 3-Bromo Acid IV.—The inhibition of the decarboxylation of the 3-bromo carboxylate ion IV is readily understandable in terms of Bordwell's mechanistic evidence, which shows that the transition state has considerable zwitterionic

character,[8] because such a transition state (essentially a zwitterion plus a bromide ion) should be considerably destabilized by transfer from water to a micellar pseudophase. On the other hand, if the transition state had considerable lactone character, one might expect the hydrophobic interactions between the micelle and the forming lactone plus those between the cationic micelle and the forming bromide ion to outweigh the energetically beneficial initial state interactions between the carboxylate ion and the cationic micelle so that the rate would not be retarded.

Catalysis of Decarboxylation of the 2-Cyano Acid II. —Although micellar catalysis is often interpreted in terms of a bringing together of reactants in a medium favorable for reaction, some unimolecular reactions are catalyzed by micelles.[3,9,11] Decarboxylations in which a carboxylate ion generates a carbanionlike transition state are strongly catalyzed by cationic micelles. The electrostatic interactions between the cationic micelle and the carboxylate ion assist the incorporation of the latter into the micelle and, of itself, this stabilization of the initial state would result in a rate reduction unless the transition state, with its delocalized negative charge, interacts more strongly with the micelle than the more localized carboxylate ion and offsets this rate reduction. As in the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion (I),[3,12] we assume that added salts enhance the CTABr-catalyzed decarboxylation of 2-cyanophenylacetate (II) by reducing the charge density of the micelle. These positive salt effects upon micellar catalysis are unusual and have been observed only for decarboxylations.[12] In all other systems the counterions inhibit catalysis, presumably by excluding an anionic reactant from the micelle.[9-11] Added salts affect micellar structure;[12,19] for example they increase aggregation number, decrease the cmc, and cause the shape of the micelle to change from spherical toward rodlike, but, for all investigated reactions other than decarboxylations, it appears that these structural changes have no direct kinetic effects. For example, in the CTABr-catalyzed hydrolysis of the 2,4-dinitrophenyl phosphate dianion there is almost no increase of rate when the surfactant concentration is increased so much that the micelle becomes rodlike.[17] Decarboxylations appear to be more sensitive to micellar catalysis than most nucleophilic substitutions, where rate enhancements are often only *ca.* 10-fold, and are rarely more than 100-fold,[9,10] as compared with the 660-fold enhancement of the decarboxylation of II at 25°, and probably they are unusually sensitive to the charge density and nature of the micellar surface. When a cyanocarboxylate ion is incorporated into a cationic micelle the negatively charged carboxylate residue will probably be in the water-rich region, where it will suffer electrostatic repulsions if added anions build up in the Stern layer, and added salts should destabilize the initial state. On the other hand, this negative charge becomes delocalized into the carbanionlike transition state where it will be closer to the quaternary ammonium groups of the surfactant and therefore relatively unaffected by anions in the Stern layer.

Registry No.—II, 34220-42-3; IV, 25297-23-8; CTABr, 57-09-0; 3-phenylpropionate ion, 826-17-5.

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Autoxidation of Esters. I. Isobutyl Acetate

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Isobutyl acetate was treated with oxygen in the temperature range 100–120°. This autoxidation reaction seems to proceed as the analogous one with isobutane, but the primary product is, apparently, much less stable. The 2-hydroperoxyisobutyl acetate decomposes to acetone, formaldehyde, and acetic acid at a rate comparable to its rate of formation. In some respects, this decomposition seems not to involve radical intermediates. The formaldehyde is readily oxidized further to formic acid. Carbon monoxide, hydrogen, isobutyric acid, and 2-oxopropyl acetate are minor products in the isobutyl acetate oxidation. The oxidation kinetics conform to the usual free-radical chain mechanism rate expression with little complication.

The reaction of hydrocarbons with oxygen is one of the most thoroughly studied[1] reactions of organic chemistry; yet, the amount of information available on oxygen-containing derivatives is surprisingly small. Aldehydes,[2] ethers,[3] and alcohols[4] are the most closely studied of the oxygen-containing compounds.

Although the oxidation of unsaturated fatty acid esters[5] has been intensively studied, information is lacking on simple esters where the ester function and the oxidatively labile hydrogen are in proximity. In particular, the autoxidative attack on the alcohol portion of an ester at the α and β positions is the major interest here.

$$\overset{\beta}{\mathrm{R}}\overset{\alpha}{\mathrm{CH_2}}\mathrm{CH_2O}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{R'}$$

1

From the few data available in the present literature it appears that trying to investigate oxidative attack

(1) Relatively recent reviews of the subject include L. Reich and S. S. Stivala, "Autoxidation of Hydrocarbons and Polyolefins," Marcel Dekker, New York, N. Y., 1969; F. R. Mayo, *Accounts Chem. Res.*, **1**, 193 (1968); J. Betts, *Quart. Rev., Chem. Soc.*, **25**, 265 (1971).

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(5) W. O. Lundberg, Ed., "Autoxidation and Antioxidants," Interscience, New York, N. Y., 1962. Several chapters deal with fatty acid autoxidation.

at the α position may be unrewarding. Although benzyl acetate[6] is moderately reactive in autoxidation to give an 80% yield of titratable hydroperoxide at 30° and gas-phase oxidation of ethyl acetate[7] at 250–400° has been postulated to occur at the α position, simple esters seem inert in the liquid phase. Buxbaum was unable to obtain any useful reaction between oxygen and ethylene dibenzoate[8] up to 200°, and isopropyl acetate[9] could not be oxidized at a reproducible rate or product yield in the temperature range 135–150°. The sensitivity of the oxidation to the purity of the ester was attributed to hydrolysis and the oxidative reactivity of isopropyl alcohol, which was much higher than the reactivity of the ester. *In situ* conversion of alcohols to borate esters[10] to protect them from further oxidative attack is a well-known technique.

Reported in this paper are the results of a detailed investigation of the liquid-phase autoxidation of isobutyl acetate, one of the simplest possible substrates where a reactive (tertiary) hydrogen is β to the ester function. This ester is a simple analog of the well-studied isobutane[11] where one methyl group has been replaced by an acetoxymethyl group. Some less complete data on the autoxidation of the bifunctional compound *trans*-1,4-cyclohexylenedimethylene diacetate are presented in another paper.[12]

Experimental Section

Materials.—Isobutyl acetate (IBAc), isobutyl benzoate (IBBz), and isopentyl acetate (IPAc) were Eastman reagent-grade materials and were distilled before use. The IBAc contained low levels (~0.5%) of either butyl acetate or ethyl isobutyrate, depending on the lot. Neither impurity at this level is expected to have an effect on the results. Methyl benzoate, used as a reaction solvent, was also an Eastman reagent-grade compound and was also distilled. Initiators were Lucidol 99% *tert*-butyl peroxide, which was used directly, or Columbia Organic 1,1′-azodicyclohexanecarbonitrile, which was recrystallized from methanol–acetone. All other materials were reagent-grade chemicals and were used directly.

2-Oxopropyl Acetate.—This material, anticipated as a possible product in the oxidation,[5] was synthesized by direct acetylation of 1-hydroxy-2-propanone (Eastman Organic Chemicals No. 10646). 1-Hydroxy-2-propanone (14.8 g, 0.2 mol) in 75 ml of pyridine was mixed with 20.4 g of acetic anhydride and allowed to stand overnight. Distillation of the mixture gave 8 g of product: bp 124–127° (150 mm) [lit.[13] bp 65° (11 mm)]; nmr ($CDCl_3$, 60 MHz) δ 2.08 (s, 6, CH_3, CH_2OOCCH_3), 4.58 (s, 2, $COCH_2OOCCH_3$). 2-Oxopropyl acetate was detected in small amounts (see Results and Discussion) in IBAc oxidations by comparison of mass spectral–glpc effluent patterns with those of the authentic material.

2-Hydroxy-2-methylpropyl Acetate (2).—This material seemed to be incompletely described in the literature; it was expected to be the major product (following reduction of the corresponding hydroperoxide) from the oxidation of IBAc. Sodium acetate (5 g) was dissolved in acetic acid (35 ml) by warming on a steam bath; then 5.0 ml of 1,2-epoxy-2-methylpropane (Columbia Organic) was added by syringe, and the mixture was kept on a steam bath for 1 hr. The reaction mixture was poured into water, sodium hydroxide solution was added until the mixture was neutral, and then the mixture was extracted with ether. Distillation of the ether extracts yielded 3.5 g of oil which, by nmr, was 85% desired product. Repetitive, preparative glpc (Carbowax 20M column) of the oil yielded 1.0 g of analytical sample used for making standard solutions for glpc calibration: nmr ($CDCl_3$, 60 MHz) δ 1.20 [s, 6, $(CH_3)_2C$], 2.05 (s, 3, $OOCCH_3$), ~3 (s, 1, $(CH_3)_2COH$], 3.88 (s, 2, CH_2OOCCH_3).

Oxidation Procedure.—Initiator and ester were made up in reaction bulbs of 54- or 104-ml capacity and shaken with oxygen at 100 or 120°. The apparatus used has been previously described, along with the procedure for calculating the rates.[14] At the conclusion of a run, in some cases, the gases in the reaction bulb void space were sampled for glpc analysis before final degassing of the bulb, detachment from the apparatus, and weighing.

Analysis Procedure.—Oxidates were titrated[15] first for hydroperoxide by the usual iodometric procedure and then for free carboxylic acid with 0.1 *N* sodium hydroxide. An approximately 25-g aliquot of the oxidate was reduced[16] with triphenylphosphine by the addition of 15% excess (as indicated by the iodometric titration) in a small amount (~2 ml) of IBAc. The reduced mixture was then distilled at ~10 mm with the pot temperature kept at 30° or less and the receiver maintained at −200°. An aliquot of the weighed distillate was made up with benzene as an internal standard and analyzed for undecomposed *tert*-butyl peroxide, acetone, and *tert*-butyl alcohol by glpc (Carbowax 20M column). The pot residue was quantitatively collected with benzene as the solvent, made up with mesitylene as an internal standard, and analyzed for **2** by glpc (Carbowax 20M). Both glpc analyses were calibrated with authentic samples. Also, sufficient pot residue from one oxidation run was collected from the glpc effluent to obtain an nmr spectrum and confirm the assigned structure of **2**. About one-sixth of the total amount of **2** was carried over into the distillate by this procedure, and the total yield of this product was corrected accordingly.

The acid products of this reaction could not be satisfactorily analyzed directly by glpc. To apportion the total yield of acid as determined by titration, the acidic fraction of an oxidation was isolated and converted to propyl esters for glpc analysis as follows. Following reduction of an oxidate sample, sufficient aqueous sodium hydroxide (0.1 *N*) was added to the mixture to convert all acids to sodium salts. The aqueous phase was isolated, washed with ether, acidified (pH 1), and continuously extracted with ether for 24 hr. The ethereal solution of acids was dried ($MgSO_4$) and concentrated to ~20 ml by distillation under reflux. The pot residue was then esterified with propanol–BF_3 reagent and worked up for glpc analysis as described.[17] Propyl formate, acetate, and isobutyrate were identified by comparison of their retention times with those of authentic samples. The effectiveness of the procedure was checked by esterifying a known mixture of the three acids in a like manner.

Results and Discussion

Most of the rate and product data of this investigation are summarized in Table I. Supplementary data are contained in Tables II and III.

Rate Law for the Oxidation. Order in Substrate Concentration.—Figure 1 shows a plot of the initial rate of oxygen consumption (R_0) *vs.* the concentration of IBAc for 120° runs where the *tert*-butyl peroxide concentration was near 0.038 *M*. For the pure methyl benzoate solvent (run 13, Table I), the observed rate was increased by the factor $(0.038/0.0128)^{1/2}$ to correct for the lower initiator concentration. As indicated, methyl benzoate, chosen because of its similar polarity to IBAc, is not completely inert under the oxidation conditions so that a cooxidation of the two esters was actually performed. A good linear correlation was obtained and indicated first-order dependence on the

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TABLE I

OXIDATION OF ESTERS[a]

Run	Charge and rate data: [*tert*-Bu_2O_2], *M*	IBAc, mmol	Volume, ml	Time, min	O_2 absorbed, mmole	$R_0 \times 10^4$,[b] *M* min^{-1}	Product yields: Total $-O_2H$,[c] mmol	Total $-COOH$,[d] mmol	$(CH_3)_2C(OH)CH_2OAc$,[e] mmol	$(CH_3)_2CO$, mmol	*tert*-BuOH, mmol
					120°						
1	0	297.0	45.7	1775	5.6	0.38[f]	1.21	6.07	1.36	2.81	
2	0	301.0	46.3	1445	3.2	0.23	1.32		1.26	1.83	
3	0.0098	297.0	45.9	495	2.7	1.2	1.25	2.23	1.09	1.00	0.32
4	0.0200	298.0	46.0	1460	13.7	1.9	0.30	17.10	2.55	~10.20	1.12
5	0.0202	598.0	92.5	495	8.4	1.9	3.05	6.75			
6	0.0375	299.0	46.0	495	4.9	2.3	1.98	3.70			
7	0.0386	297.0	46.0	410	4.9	2.5	1.71	3.66	1.81	2.56	0.74
8	0.0391	597.0	92.6	410	9.6	2.7	3.41	7.71			
9	0.0400	300.0	46.2	1200	7.5	2.5	0.37	8.02			
10	0.0908	299.0	46.7	275	5.2	4.2	1.99	4.05			
11[g]	0.0375	148.0[g]	45.0[g]	505	2.9	1.5	1.15	2.30			
12[g]	0.0381	76.3[g]	45.2[g]	475	1.8	1.0	0.63				
13[g]	0.0128	0[g]	42.9[g]	400	~0.3	0.22	0.10				
14[h]	0.0167	299.0	56.2	170	8.3	~9.8	0.23				
15[i]	0.0213	299.0	48.4	360	4.6	1.3	1.83	3.15	1.07	0.90	0.58
16[j]	0.0394	299.0	47.5	410	5.8	2.9	2.38				
17[k]	0.0423	223.0[k]	44.1	495	3.6	2.4	1.82	3.04			
18[l]	0.0404	265.0[l]	46.5	85	4.0	11.5	1.93	1.35			
					100°						
19	0.0400	299	44.9	2110	2.5	0.30	1.24	1.97	1.34	0.75	0.43
20	0.0423	299	45.0	1830	2.7	0.38	1.12	2.26	1.14	1.14	0.47
21	0.0790	299	45.3	1510	3.1	0.45	1.23	2.48	1.32	1.15	0.65
22	0.0402[m]	299	44.6	225	5.9	9.2	2.00	3.42			
23[n]	0.0403	277	47.1	1525	7.0	1.4	−0.80[o]				

[a] Oxygen pressures ranged from 3 to 6 atm. [b] Initial oxygen uptake rate. [c] By iodometric titration. [d] By base titration. [e] After triphenylphosphine reduction. [f] Final (steady from t = 1300 min to end), rate = 0.88 *M* min^{-1}. [g] Methyl benzoate solvent. [h] 104.0 mmol of acetic anhydride present. [i] 21.7 mmol of isobutyl alcohol in initial charge. [j] 1.0 ml of water (58 mmol), added at start gives single phase at the 120° reaction temperature. [k] Isobutyl benzoate. [l] Isopentyl acetate. [m] 1,1′-Azodicyclohexanecarbonitrile initiator. [n] 47.5 mmol of *tert*-butyl hydroperoxide was added. [o] Net decrease in $-O_2H$ titer.

TABLE II

ACID CONTENT OF ISOBUTYL ACETATE OXIDATIONS AT 120°

Run	[*tert*-Bu_2O_2], *M*	IBAc, mmol	Time, min	O_2 consumed, mmol	Convn, %	Total $-O_2H$, mmol	Total $-COOH$, mmol	Acid yield, mol % of total: HCOOH	CH_3COOH	$(CH_3)_2CHCOOH$
24	0	600	1400	7.5	1.25	2.50	6.45	18.2	77.5	3.8
25	0.024	373	1125	13.8	3.70	1.37	16.41	20.5	75.3	4.2

TABLE III

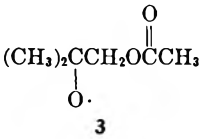
GAS YIELDS OF ISOBUTYL ACETATE OXIDATIONS AT 120°

Run	O_2 consumed, mmol	Convn, %	Gas yields, mmol: CO	H_2
4	13.7	4.60	3.80	1.89
3	2.7	0.91	0.34	0.10
7	4.9	1.65	0.82	0.06
8	9.6	1.61	1.30	0.20
24	7.4	1.23	0.72	0.13
17[a]	3.6	1.61	0.54	0.02
18[b]	4.0	1.51	0.09	0.01
25	13.8	3.70	4.21	0.89

[a] Isobutyl benzoate. [b] Isopentyl acetate.

IBAc concentration; it further indicated that the oxidation is not sensitive to participation by solvent-derived radicals; *i.e.*, an ideal cooxidation[18] is obtained. Active tertiary hydrogen substrates, in particular cumene,[19] often show marked deviation from ideality.

These results also suggest that this system is significantly different from the analogous isobutane[11] oxidation where the *tert*-butylperoxy radical enters into a bimolecular, nonterminating reaction to produce *tert*-butoxy radicals. At high IBAc concentration, **3** would be converted to **2**.



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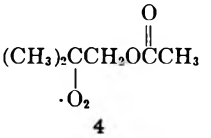

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The possibility of the conversion of the chain carrier radical **4** to **3** as a significant reaction in the mechanism is discussed in the section on products. A comparison of the absolute oxidation rates of the IBAc and isobutane systems infers that a much faster termination exists in the IBAc system than in the isobutane system. At 100° with *tert*-butyl peroxide (0.0619 *M*), neat isobutane (7.46 *M*) oxidizes[11] at a rate of 3.5×10^{-4} *M* min^{-1}. At the same temperature and comparable initiator concentration (run 21, Table I), neat IBAc (6.6 *M*) oxidizes at 0.45×10^{-4} *M* min^{-1}.

Order in Initiation Rate.—In Figure 2 the oxidation

(18) F. R. Mayo, M. G. Syz, T. Mill, and J. K. Castleman, *Advan. Chem. Ser.*, **75**, 38 (1968).

(19) G. A. Russell, *J. Amer. Chem. Soc.*, **78**, 1047 (1956).

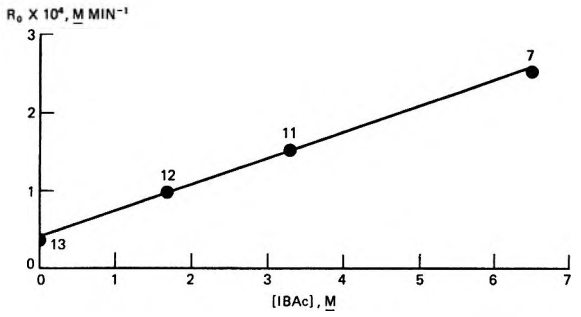


Figure 1.—Substrate concentration rate dependence.

rates of neat (6.5 *M*) IBAc at 120° are plotted against the initiator concentrations on a log–log scale. A straight line is obtained over a tenfold range of *tert*-butyl peroxide concentration, and the slope of the line is 0.52, probably identical within experimental error to the theoretical value of $^1/_2$ which applies for simple oxidations. Thus, some of the complications which lead to nonrational[20] initiation orders are absent in this reaction.

In particular, the thermal initiation rate is apparently minor compared to that from the added *tert*-butyl peroxide. The estimation of the initial thermal rate, 0.3×10^{-4} *M* min^{-1} (runs 1 and 2, Table I), suggests that, where *tert*-butyl peroxide is ~0.02 *M*, the ratio of initiation rates is $(1.9/0.3)^2 = 40/1$. Also, the onset of autocatalysis is relatively slow with the rate of the thermally initiated run slowly rising to $\sim 0.88 \times 10^{-4}$ *M* min^{-1}. Initiated oxidations of IBAc at 120° show either no autocatalysis or a slight diminution of rate, as shown by Figure 3. These results contrast with the oxidation of the cyclohexylenedimethylene diacetate, described in another paper.[12]

Temperature Effect.—Only two temperatures were investigated due to the low reactivity of IBAc. At 100° with *tert*-butyl peroxide (0.0400 *M*), the rate is 0.30×10^{-4} *M* min^{-1} (run 19, Table I) *vs.* the expected rate of 2.7×10^{-4} *M* min^{-1} (read from Figure 2) at 120°. A two-point Arrhenius plot of these data indicates an overall activation energy (E_a) of 32 kcal/mol. Assuming the rate law is of the form

$$R_0 = K[tert\text{-}Bu_2O_2]^{1/2}[IBAc] \quad (1)$$

and the activation energy[21] for *tert*-butyl peroxide is 37 kcal/mol, the overall activation energy exclusive of the initiation step is

$$\Delta E = 32 - (^1/_2)(37) = 14 \text{ kcal/mol}$$

If, as argued in the preceding sections, the termination is the relatively low activation process of a primary (or secondary) and a tertiary peroxy radical combination (E_a ~3), then the net activation energy of the propagation reaction would be ~15 kcal/mol. This assumes that eq 1 in the complete form is

$$R_0 = (R_i/2k_t)^{1/2}k_p[IBAc] \quad (2)$$

where k_p is the rate constant for propagation, k_t the rate constant for termination, and R_i the rate of initiation, related to the concentration of *tert*-butyl peroxide by

$$R_i = 2k_d[tert\text{-}Bu_2O_2] \quad (3)$$

where k_d is the rate constant for the decomposition of *tert*-butyl peroxide. The 15-kcal activation energy

(20) D. E. Van Sickle, *J. Org. Chem.*, **37**, 755 (1972).

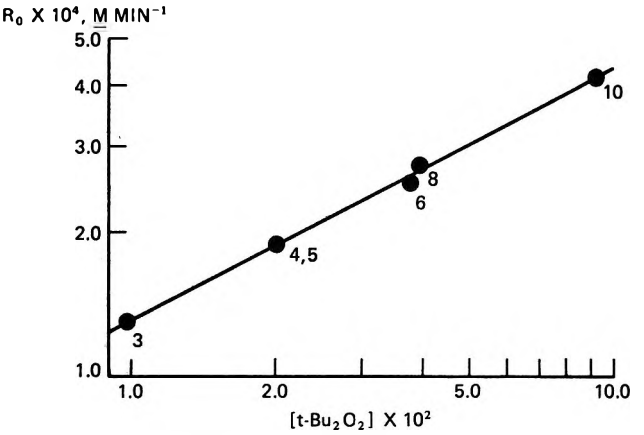


Figure 2.—Effect of initiator concentration.

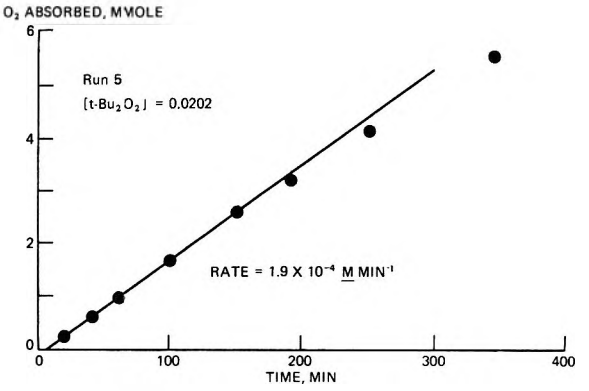
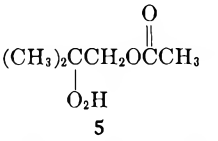


Figure 3.—Oxygen absorption of isobutyl acetate.

associated with k_p is the same value calculated for the isobutane[11] oxidation.

Products of Oxidation.—As can be seen from Table I, hydroperoxide yields are only ~40% of the oxygen absorbed. After triphenylphosphine reduction of the oxidate, the amount of **2** found corresponds quite closely to the hydroperoxide content. Therefore, it was assumed that, at most of the conversions studied, the hydroperoxide **5** accounted for ~40% of the oxygen consumed.



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Only in the high conversion run 145 (Table I), where reaction was continued until oxygen in the bulb void space was exhausted, did **2** substantially exceed the hydroperoxide yield.

Aside from *tert*-butyl alcohol, which arises from initiator fragments, the only other product reliably detected in the glpc analysis was acetone. Peaks which were later identified as those of acetic and isobutyric acids were present but did not account quantitatively for the acid titrated. Calculation of the amount of *tert*-butyl alcohol which should be formed if all peroxide which decomposes is converted to this product agrees within 0.1 to 0.2 mol of alcohol actually found. Previously published[21] values for the decomposition rate of *tert*-butyl peroxide were used to calculate the number of *tert*-butoxy radicals formed. Therefore, all of the

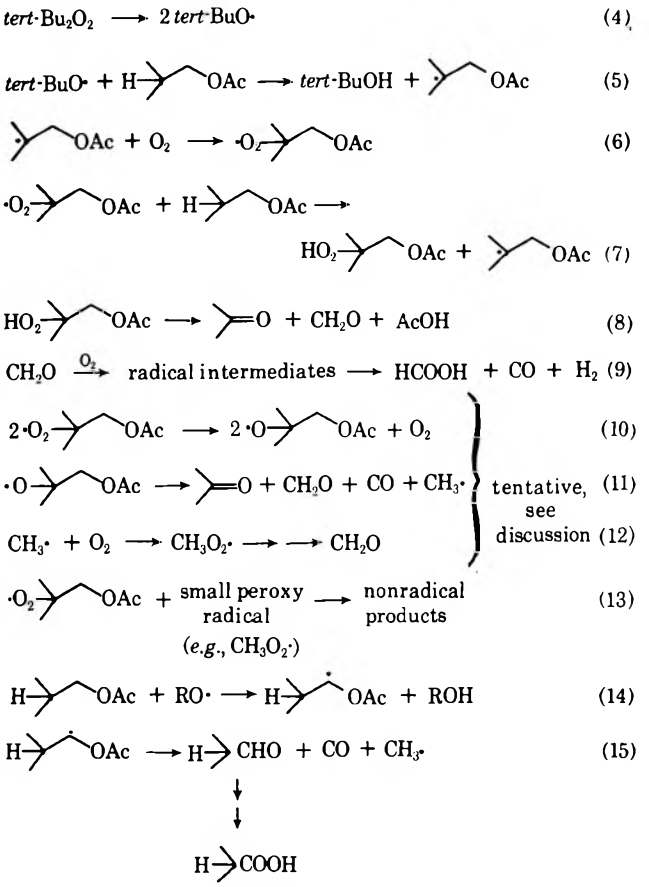
(21) P. Molyneux, *Tetrahedron*, **22**, 2929 (1966), and references cited therein. The "best" value of E_a for *tert*-butyl peroxide is 37.8 ± 1.0 kcal/mol.

acetone found in the IBAc oxidations was assigned to the substrate itself and not to fragmentation of the *tert*-butoxy initiator radicals.

As indicated previously, direct glpc analysis for the acids present in the product mixture was not effective. To determine the nature of the acids present, two oxidation runs were made which were worked up to isolate the acids present as propyl esters (see Experimental Section). The results are summarized in Table II. The significance of the results is considered in the section on the mechanism of the reaction.

Gas yields of selected runs are given in Table III. The gas law was used to calculate the yields from the glpc analysis of the gas from the reaction bulb void. The amount of product gas dissolved in the liquid phase was calculated from the estimated[22] solubilities of the gases in the isobutyl acetate. The only two significant gaseous products were carbon monoxide and hydrogen. Carbon dioxide was reported only in trace quantity.

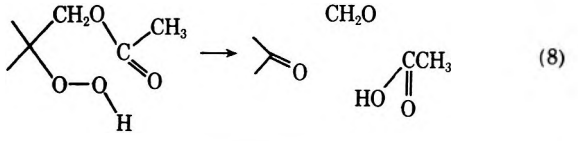
Proposed Mechanism.—It appears from the data presented here that isobutyl acetate oxidizes by the same mechanism as isobutane[11] but that subsequent decomposition of the product hydroperoxide complicates the overall picture. The following equations represent a minimum description of the system.



Except for the final two equations, all products are postulated to arise from attack at the tertiary hydrogen. Equations 4–7 are a straightforward analogy of the hydrocarbon oxidation mechanism.[1] The remaining equations require some elaboration and qualification.

Equation 8.—Decomposition of hydroperoxides[23] is usually thought to proceed *via* radical intermediates; yet the characteristics of this reaction seem to require, at least in part, a nonradical decomposition. Autocatalysis of the oxidation is very weak, which suggests that unimolecular or bimolecular decomposition to radicals is not obtained. An induced form of decomposition which would not result in a net generation of radicals as occurs with *tert*-butyl hydroperoxide[23] (eq 10 in part) cannot be a major contributor since little or no excess of **2** over the amount of hydroperoxide reduced is found. This conclusion is qualified on the assumption that peracids make no contribution to the hydroperoxide titer.

A brief investigation of the decomposition properties of the hydroperoxide was made by isolating (by distillation of unreacted IBAc) 1.46 mmol of **5**, adding IBAc until there was 40 ml of solution, and decomposing it at 120°. Within 16.25 hr, all of the hydroperoxide had decomposed, and 1.37 mol of acetone and 0.82 mol of acid had formed. More importantly, none of the acetate **2** was detected in the products. Thus, if radical **3** is formed, it rapidly fragments without competing abstraction from IBAc solvent to give **2**. Although we have no conclusive evidence, a cyclic transition state for decomposition looks attractive.



Equation 9.—Formic acid is a significant product of the reaction, and it seems reasonable to ascribe its formation to the oxidation of formaldehyde. The amount of formic acid found is significantly less than the amount of acetic acid; if formaldehyde and acetic acid are formed initially in equal amounts, conversion to formic acid is not quantitative. A possible explanation for this less than quantitative conversion is transesterification with the substrate to give isobutyl formate and acetic acid. Alternate reactions of formaldehyde include formation of peroxy acetals (with hydroperoxides) and subsequent decomposition. No significant levels of formaldehyde were detected by the chromotropic acid test during the oxidations or the hydroperoxide decomposition experiment. In run 16 (Table I) polarographic analysis of the water phase which separated on cooling gave some indication of formaldehyde. Another possibility for less than quantitative conversion of formaldehyde to formic acid could be the concomitant formation of carbon monoxide. Horner, Style, and Summer[24] studied the photooxidation of formaldehyde in the gas phase at 110° and found formic acid, carbon monoxide, carbon dioxide, and hydrogen as products. No analogous liquid phase studies seem to be available.

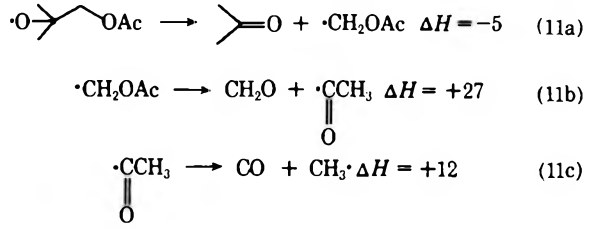
Equations 10–12.—As pointed out previously, an induced decomposition of the hydroperoxide does not seem to be the major pathway for its decomposition. A seemingly plausible alternate explanation for the formation of carbon monoxide, a significant product,

(22) Solubilities of 0.0088 and 0.0022 mol $l.^{-1}$ atm^{-1} for carbon monoxide and hydrogen, respectively, were calculated by the method of J. M. Prausnitz and F. H. Shair, *Amer. Inst. Chem. Eng. J.*, 682 (1961).

(23) R. Hiatt, T. Mill, and F. R. Mayo, *J. Org. Chem.*, **33**, 1416, 1421 (1968).

(24) E. C. A. Horner, D. W. G. Style, and D. Summers, *Trans. Faraday Soc*, **50**, 1201 (1954).

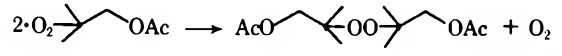
could be the decomposition of radical **3** (eq 11). However, a theoretical difficulty of eq 11 is the apparent endothermicity of the reaction. Calculation[25] of the thermodynamics of eq 11 suggests that the reaction is 34 kcal endothermic! If the reaction is broken down in steps the following results are obtained.



These results suggest that the reaction may not proceed beyond the first step and that $\cdot CH_2OAc$ is degraded to carbon monoxide and other products *via* the associated peroxy radical $\cdot O_2CH_2OAc$. Reactions of this radical are not known.

Evidence that radical **4** does form includes the detection of small amounts of 2-oxopropyl acetate in the product mix. Thus, for this product to form, methyl instead of acetoxymethyl is cleaved from radical **4**. The amount of 2-oxopropyl acetate formed is small, obscured in the glpc trace by acetic acid, and is estimated to be present in less than $^1/_{20}$ the amount of **2**.

Equation 13.—As discussed in the section on rates, the termination reaction does not seem to be between two type **4** radicals.



Reactions of this type (between tertiary radicals) have relatively high activation energies,[26] and the overall rates of oxidation are sensitive to the addition[19] of small amounts of reactive substances. With the various fragments available from the decomposed hydroperoxide, a cross termination seems most likely.

Equations 12 and 13.—As mentioned in the introduction, it has usually been assumed that hydrogens α to an esterified hydroxyl function are inert to attack by peroxy radicals. Thus, ethylene dibenzoate could not be oxidized[8] at temperatures below 200°, and Mill[9] found isopropyl acetate quite resistant to oxidation but, perhaps, susceptible to water catalysis. The experiments with added water (run 16, Table I) or isobutyl alcohol (run 15, Table I) suggest that IBAc oxidation rates seem comparable to those of the "undoped" runs, and the acid yield of the run with isobutyl alcohol seems normal. Thus, rapid oxidation of the alcohol, relative to the oxidation rate of the ester, does not seem to be part of the mechanism. Hydrolysis of the ester apparently is slow; when the reaction mixture of run 16 (Table I) was cooled, water separated from the reaction in apparently the same amount started with. However, isobutyric acid is a significant product of the ester oxidation and needs to be accounted for. The most direct route to this product seems to be attack of the α position of the ester by some relatively reactive radical, most likely an alkoxy radical. Either decomposition of the ester radical as shown or, perhaps, degradation of the associated peroxy radical should ultimately lead to isobutyric acid.

Oxygen Balance.—The fact that secondary products are so prominent in the IBAc oxidation, even at 1% conversion, complicates accounting for the oxygen consumed. However, a reasonable approximation is to assume that the acetate **2** plus the acetone represent the total amount of hydroperoxide **5** originally formed. The difference between this amount of oxygen and the amount actually consumed represents the secondary oxidation processes, *e.g.*, conversion of formaldehyde to formic acid. Two quantities were determined in Table IV. The "excess oxygen" (ΔO_2) represents the oxygen available for secondary oxidation processes, and the "excess acid" (A_2) is the acid assumed to be present besides the acetic acid. Except for the first entry in the $A_2/\Delta O_2$ column, the ratio of "excess acid" to "excess oxygen" is ~2 and suggests the stoichiometry of eq 16.

TABLE IV

OXYGEN BALANCE FOR ISOBUTYL ACETATE OXIDATION[a]

Run	Acetone and diol	O_2	ΔO_2[b]	Acid − acetone = A_2[c]	$A_2/\Delta O_2$
		100°			
19	2.09	2.5	0.4	1.22	3.0
20	2.05	2.7	0.6	1.12	1.9
21	2.24	3.1	0.8	1.33	1.7
		120°			
1	3.94	5.6	1.7	3.26	1.9
3	2.09	2.8	0.7	1.23	1.8
7	4.37	4.9	0.5	1.10	2.2

[a] All quantities in millimoles. [b] "Excess oxygen." [c] "Excess acid."

$$2CH_2O + O_2 \longrightarrow 2HCOOH \qquad (16)$$

This treatment overlooks the formation of isobutyric acid as well as carbon monoxide and also predicts a 1:1 relationship between formic and acetic acid, a fact not borne out by the data of Table II.

Other Esters.—Preliminary experiments were carried out on isobutyl benzoate and isopentyl acetate. As expected, the oxidation behavior is mostly independent of the acid part of the ester. However, placing one more methylene group between the active hydrogen and the ester function causes the oxidation to more nearly resemble that of the hydrocarbon. Thus, isopentyl acetate oxidizes *ca.* five times as fast as isobutyl acetate, and the acid and gas yields are sharply reduced.

Registry No.—Isobutyl acetate, 110-19-0.

(25) S. W. Benson, "Methods for the Estimation of Thermochemical Data," Wiley, New York, N. Y., 1968. The thermodynamics of eq 11c can be confirmed by the data of R. Walsh and S. W. Benson, *J. Phys. Chem.*, **70**, 3751 (1966).

(26) D. G. Hendry, *J. Amer. Chem. Soc.*, **89**, 5433 (1967).

Autoxidation of Esters. II. Cyclohexylenedimethylene Diacetate

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trans-1,4-Cyclohexylenedimethylene diacetate (CHDMDA) was reacted with oxygen in the temperature range 100–120°. The data obtained from this investigation indicate that CHDMDA is more reactive in autoxidation and gives a much more complicated mixture of oxidation products than the acyclic analog (isobutyl acetate). The oxidation of CHDMDA at 100° is strongly autocatalytic, and the rate is nearly independent of added *tert*-butyl peroxide initiator. Titratable hydroperoxide accounts for ~10% of the oxygen consumed during autoxidation, but carboxylic acid yield is relatively high. Products tentatively identified from the oxidation mixture are 4-oxocyclohexylmethyl acetate (**4**) and the cis–trans pair of 1-hydroxy-1,4-cyclohexylenedimethylene diacetate (**6**).

In a previous paper,[1] it was shown that a tertiary hydrogen β to the ester function on the alcohol moiety reacts with oxygen in much the same way a hydrocarbon hydrogen does. However, the hydroperoxide formed as a primary product of ester autoxidation seemed to be much more susceptible to decomposition than a simple, tertiary hydroperoxide. To determine the effect of placing the reacting tertiary hydrogens in a ring and to determine how a bifunctional substrate would react in autoxidation, the reaction of *trans*-1,4-cyclohexylenedimethylene diacetate (CHDMDA) with oxygen was studied.

Experimental Section

Materials.—*trans*-1,4-Dimethylcyclohexane (99% pure) was obtained from Chemical Samples Co. *tert*-Butyl peroxide (99% pure) was obtained from Wallace and Tiernan, Inc., Lucidol Div. (Both materials were used as obtained.) Peroxyacetic acid was obtained from FMC Corp.

***trans*- and *cis*-1,4-Cyclohexylenedimethylene Diacetate (CHDMDA).**—The Eastman *trans*-1,4-cyclohexanedimethanol (CHDM) used was recrystallized once from ethyl acetate to give 99.4% *trans*-CHDM as indicated by glpc. The recrystallized CHDM was acetylated with acetic anhydride, and the CHDMDA was recrystallized from a water–methanol solution for a net yield of 89%. After the product was thoroughly dried in a vacuum desiccator, a 70° melting point was obtained (lit.[2] mp 70°).

The Eastman practical grade CHDM used was distilled at 6.0 mm (95% reflux on ~100-plate column) to obtain the cis isomer. The head temperature of the column was 135° [lit.[3] bp, trans, 284° and, cis, 288° (760 mm)]. A pot residue from one of these distillations (90% cis as indicated by glpc) was exhaustively acetylated with acetyl chloride–pyridine reagent to give an oil, bp 107–108° (0.5 mm) [lit.[4] bp 156° (6.0 mm)].

Cyclohexylmethyl Acetate (CHMA).—The Eastman reagent grade cyclohexane-methanol used was acetylated with acetyl chloride–pyridine reagent to yield CHMA, bp 52–54° (2 mm) [lit.[5] bp 105° (56 mm)]. Glpc indicated that the product was free of alcohol but contained ~1% of unidentified impurity.

Possible CHDMDA Oxidation Products.—Two possible CHDMDA oxidation products were synthesized as glpc standards. 4-Oxocyclohexylmethyl acetate (**4**), bp 76–78° (0.08 mm), was obtained by ozonolysis in acetic acid followed by reduction with powdered zinc of 4-*exo*-methylenecyclohexylmethyl acetate (yield ~40%). The starting acetate, bp 72–73° (2.8 mm), was obtained by acetylating the corresponding alcohol (4-methylenecyclohexane–methanol)[2] with pyridine–acetic anhydride reagent (yield ~75%). (It was confirmed that no isomerization to the methylcyclohexene derivative had occurred.) The nmr spectrum of the product agrees with the proposed structure **4**: nmr ($CDCl_3$) δ 1.0–2.1 (m, 5, ring protons), 2.1–2.5 (m, 4, ring protons), 1.98 (s, 3, methyl protons), and 3.95 (d, 2, methylene protons).

1-Hydroxy-1,4-cyclohexylenedimethylene diacetate (**6**) was obtained as a crude mixture of isomers by epoxidizing 4-*exo*-methylenecyclohexylmethyl acetate with peroxyacetic acid in the presence of sodium acetate (1g). Peroxyacetic acid (6.7 g, ~45 mmol) was added to the acetate (7.24 g, ~43 mmol) in 50 ml of acetic acid containing 1 g of sodium acetate. After the heat of the initial reaction subsided, the mixture was heated on a steam bath for ~30 min, then cooled to 0°. The crystallized sodium acetate was filtered off, and the acetic acid was evaporated with a nitrogen stream at 100° to give a thick oil (6.3 g) which would not crystallize.

The infrared spectrum of the oil showed a strong hydroxyl absorption at 3500 cm^{-1} and a strong carbonyl absorption (from the acetate groups) at 1750 cm^{-1}. Glpc showed that the oil contained principally two components (partially resolved on an XE-60 silicone column) whose retention times were identical with those of two products from the oxidation of CHDMDA. An attempt by repetitive, preparative glpc to isolate the two components was unsuccessful; nmr spectra of the trapped effluent showed considerable vinyl proton signals which suggested dehydration of products on the column. The nmr spectrum of the crude oil was in agreement with the assigned structure of a cis–trans pair but was not conclusive because of the impurities present: nmr ($CDCl_3$) δ 0.8–2.1 (m, 15, ring and methyl protons), 3.8–4.1 (m, 3.7, methylene protons), and 3.0 (s, 1, hydroxyl proton). No vinyl hydrogens were indicated.

Oxidation Procedure.—The apparatus and its use were the same as in the preceding investigation.[1] The oxidation mixtures (substrate and initiator) were made up in the reaction bulb. The *trans*-CHDMDA was added as a melt. The bulb contents, after oxidation, were emptied as a melt and soldified into a cake, and the cake was pulverized for analysis. Corrections of pressure readings and calculations of rates were done as previously described.[1]

Product Analysis.—Iodometric titrations of oxidized CHDMDA were performed by the method of Mair and Graupner.[6] Benzene solutions of oxidized *trans*-CHDMDA were analyzed (without prior triphenylphosphine reduction since the hydroperoxide titers were so low) for products by glpc using temperature-programmed XE-60 silicone columns. Docosane was added to the solutions as internal standard. No response factors were determined; so the assumption that peak area is proportional to the weight of the material was used.

Results and Discussion

The rates of oxidation of *trans*-CHDMDA and related compounds, as well as the products of oxidation, are listed in Table I.

Rates.—Qualitatively, *trans*-CHDMDA is much more reactive to oxygen than is isobutyl acetate. At 100°, R_0 (initial and final rate of oxidation) for *trans*-CHDMDA is similar to R_0 for isobutyl acetate at 120°. However, the insensitivity of the CHDMDA oxidations

(1) D. E. Van Sickle, *J. Org. Chem.*, **37**, 1392 (1972).
(2) G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, **404** (1953).
(3) Eastman Chemical Products, Inc., Technical Data Sheet No. X-105, p 2.
(4) J. Falbe, N. Huppes, and F. Korte, *Brennst. Chem.*, **47**, 207 (1966).
(5) A. MacLachlan, *J. Org. Chem.*, **29**, 1598 (1964).
(6) R. D. Mair and A. J. Graupner, *Anal. Chem.*, **36**, 194 (1964).

TABLE I

OXIDATION OF *trans*-CHDMDA AND RELATED COMPOUNDS[a]

Run	Substrate, mmol	*tert*-Bu_2O_2, *M*	Initial R_0,[b] *M* $min^{-1} \times 10^4$	Final R_0,[c] *M* $min^{-1} \times 10^4$	Time, min	O_2 consumed, mmol	O_2H yield— Mmol[e]	O_2 consumed, %	Acid,[d] mmol	Products, mmol— 4[f]	6[f]	Other[f,g]
1[h]	CHDMDA 93.5	0.0218	5.9	17.3	125	3.1	0.35	11	1.8	0.20	0.32	0.34
2	CHDMDA 93.5	0.0129	0.6	1.5	520	1.0	0.21	21	0.65	0.09	0.22	0.20
3	CHDMDA 95.5	0.0214	1.2	~1.8	510	1.3	0.14	11	0.69	0.12	0.17	0.17
4	CHDMDA 98.7	0.0462	0.9	2.1	760	2.7	0.21	8	1.3	0.19	~0.40	0.36
5	CHDMDA 95.7	0.1610	1.1	3.7	1495	6.4	0.36	5.7	4.0	0.38	0.72	1.0
6	CHDMDA[i] 98.9	0.0228	0.32	0.32	1840	1.4	0.83	60	0.42			
7	CHMA 119	0.0225	0.55	0.71	1555	1.9	1.11	59	0.54			
8	$(CH_3)_2$-C_6H_{10} 133	0.0236	1.9	4.6	355	2.2	1.93	89	0.10			

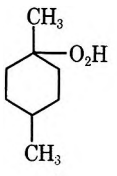
[a] Oxidations of neat materials; approximate concentrations at reaction temperature were 4–6 *M*; oxygen pressure ranged from 2 to 6 atm; 100° unless otherwise noted. [b,c] Initial and final rates of oxygen consumption, respectively, in mol $l.^{-1}$ min^{-1}. [d] By titration with aqueous NaOH. [e] By iodometric titration.[5] [f] Determined by glpc. [g] Mostly four products which elute after 6. [h] 120°. [i] Cis isomer.

to added *tert*-butyl peroxide precludes a quantitative comparison of the reactivities of CHDMDA and isobutyl acetate. Aside from run 2, in which the lowest *tert*-butyl peroxide concentration was used, the rate of oxidation was effectively zero order in initiator. Apparently, at 100°, *tert*-butyl peroxide provided only a small amount of the total radical generation.

At both 100 and 120°, the autocatalysis was strong with the final rate (after 1 to 5% conversion) being two or three times as fast as the initial rate. Evidently, and unlike that of the isobutyl acetate system, the decomposition of the primary product **1** proceeds through radical intermediates.

cis-CHDMDA oxidizes much slower than the trans isomer and without autocatalysis. No simple explanation is apparent. The CHMA (run 7) is about as reactive as the *trans*-CHDMDA on a per-tertiary-hydrogen basis.

Products.—Probably the most notable feature of the *trans*-CHDMDA oxidations is the very low hydroperoxide yield. The average value of the somewhat erratic yield is about 10%. As far as can be determined, the thermal instability of the expected *trans*-CHDMDA oxidation product **3** is unique to its structure. The oxidation of the hydrocarbon analog (1,4-dimethylcyclohexane) of CHDMDA is reported to give nearly quantitative yields of the hydroperoxide (at 95°), at least up to 10% conversions.[7] It has also been reported that 1,4-dimethylcyclohexane gives a "normal" oxidation product[8] (**1**) without participation



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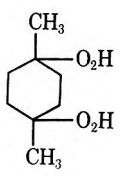
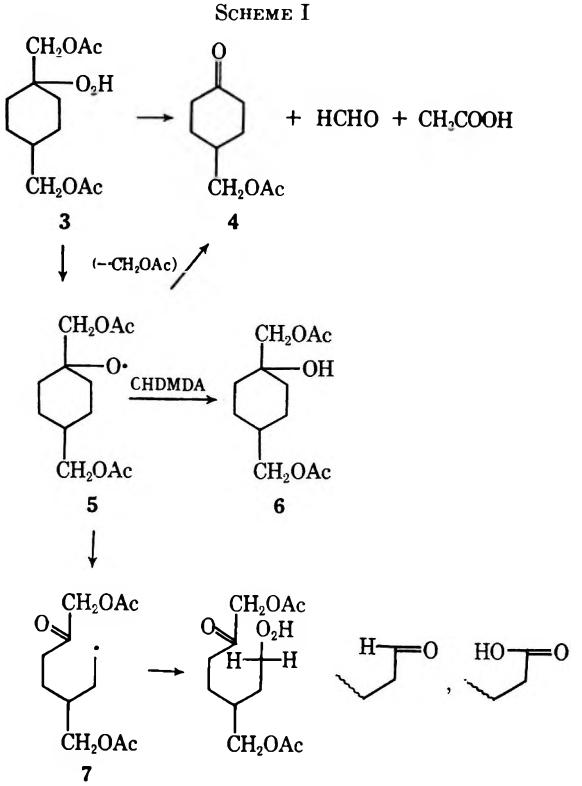


2

SCHEME I



of an intramolecular propagation step.[9] The dihydroperoxide **2** of 1,4-dimethylcyclohexane can be formed, however, with **1** being an intermediate.

In run 8, the initial oxidation rate of 1,4-dimethylcyclohexane was faster than the corresponding CHDMDA rate (run 3), and rate acceleration was fairly rapid. However, titratable hydroperoxide yield was high (although not so quantitative as previously reported[6]) and acid yield was low. Substitution of acetate groups on the methyl groups of the hydrocarbon obviously has a profound effect on the course of oxidation.

(7) V. Stannett, A. E. Woodward, and R. B. Mesrobian, *J. Phys. Chem.*, **61**, 360 (1957).

(8) R. Criegee and P. Ludwig, *Erdöel Kohle*, **15**, 523 (1962).

(9) F. F. Rust, *J. Amer. Chem. Soc.*, **79**, 4000 (1957).

The products of *trans*-CHDMDA oxidation which were identified support the premise of hydroperoxide **3** and its associated alkoxy radical **5** as major intermediates (Scheme I).

Whether **5** arises from thermolysis of **3** or from a nonterminating reaction of peroxy radicals during the oxidation cannot be determined with the limited data of this investigation. The rapid autocatalysis of the oxidation and the near zero order in added initiator suggest a facile cleavage of **3** to radicals. The unidentified products found by the glpc analysis are assumed to result from ring cleavage of radical **5** to radical **7** and so on or, possibly, from radical attack at the secondary ring hydrogens of the CHDMDA.

The amount of acid titrated in the oxidized *trans*-CHDMDA mixture increases almost proportionately to increasing conversion. However, the production of **4** falls far short of accounting for the acid formed (top line of Scheme I), even if it is assumed that the formaldehyde is quantitatively oxidized to formic acid.[1] Clearly, there are other sources of carboxylic acid in the oxidation mechanism.

The results of this and other investigations indicate that a multiplicity of products may be generated from the autoxidation of simple bifunctional esters. Much more work will be required to identify and authenticate all of the elementary steps of the oxidation mechanism of esters.

Registry No.—**4**, 33904-15-3; *trans*-1,4-cyclohexylenedimethylene diacetate, 10412-78-9; 4-*oxo*-methylenecyclohexylmethyl acetate, 33904-17-5.

Resin Acids. XXIII. Oxidation of Levopimaric Acid with Potassium Permanganate and Osmium Tetroxide[1,2]

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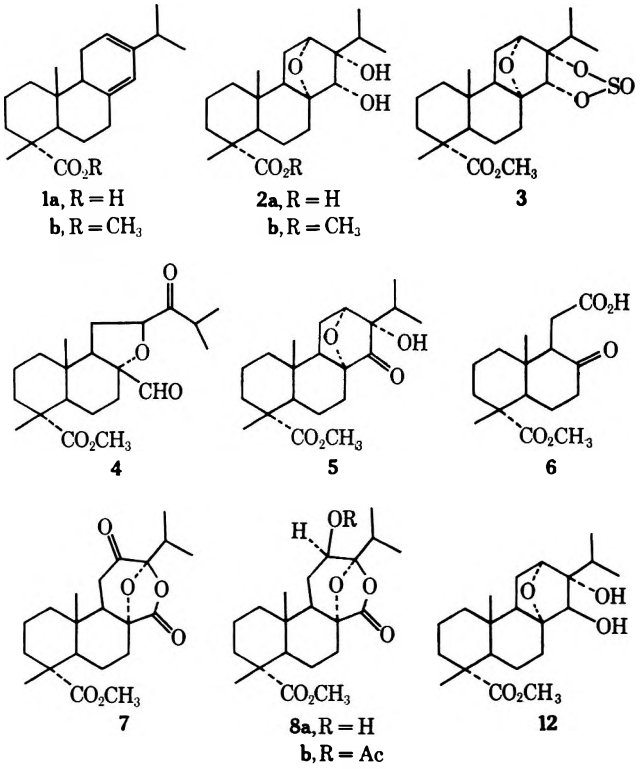
Structures have been deduced for the products resulting from the $KMnO_4$ and osmium tetroxide oxidation of levopimaric acid. The major product of $KMnO_4$ oxidation is 8α(12α)-oxido-13α,14α-dihydroxyabietan-18-oic acid (**2a**). The compounds produced by osmium tetroxide of methyl levopimarate are methyl 8α,14α-dihydroxyabiet-12-en-18-oate (**16**), methyl 12α,13α-dihydroxyabiet-8(14)-en-18-oate (**13**), and methyl 8α,12α,13α,14α-tetrahydroxyabietan-18-oate (**15**). The preparation of other enediols, epoxydiols, and tetraols derived from levopimaric acid is described.

Structure **2a** (exclusive of stereochemistry) was proposed after prolonged controversy[3] by Wienhaus and Marchand[4] for the major product resulting from the oxidation of levopimaric acid (**1a**) with aqueous permanganate. This formula has been generally accepted, but the evidence for the gross structure was not decisive and the stereochemistry assigned to it more recently on a provisional basis[5] remained unproved.[6] In the present communication we produce conclusive proof for formulation of this substance as **2a**. We also show that earlier structure assignments[8] for the diols obtained by osmylation of methyl levopimarate (**1b**) require correction.

Potassium Permanganate Oxidation.—The nmr spectrum of **2b**, obtained in 30% yield by oxidation of levopimaric acid followed by esterification, was in excellent agreement with the gross structure assigned to it by the German workers.[4] The presence of a secondary hydroxyl group on a carbon next to two tertiary centers and of an ether oxygen linking a tertiary and secondary carbon atom next to a methylene group was indicated by a doublet (J = 3 Hz) at 4.05 ppm, which collapsed to a singlet on addition of D_2O, and a multiplet at 3.30 ppm. The cis nature of the diol was easily established by the formation of a sulfite ester



(1) Previous paper: W. Herz and V. Baburao, *J. Org. Chem.*, **36**, 3899 (1971).

(2) Supported in part by grants from the National Science Foundation (GP-12582) and the Petroleum Research Fund, administered by the American Chemical Society (508-A1).

(3) For a review of work prior to 1953, see J. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, 2nd ed, Cambridge University Press, New York, N. Y., 1952, p 438; Vol. V, 1957, pp 604–610.

(4) H. Wienhaus and B. Marchand, *Chem. Ber.*, **91**, 401 (1958).

(5) H. Kanno, W. H. Schuller, and R. V. Lawrence, *J. Org. Chem.*, **31**, 4138 (1966).

(6) Especially so since the structure of levopimaric acid dioxide, whose transformation products were compared with the transformation products of **2a**, has had to be revised.[7]

(7) W. Herz, R. C. Ligon, H. Kanno, W. H. Schuller, and R. V. Lawrence, *J. Org. Chem.*, **35**, 3338 (1970).

(8) B. Marchand, *Chem. Ber.*, **91**, 407 (1958).

3 and by facile cleavage of 2b with lead tetraacetate to a product which had properties commensurate with formula 4. The nmr spectrum of 4 displayed the signal of the C-10 methyl group at relatively high field. This value is reasonable if the C-10 methyl group is in a 1,3-diaxial relationship to the new aldehyde carbonyl, a situation possible only if the oxide bridge of 2b is α oriented.

To confirm this deduction and to establish the relative orientation of the hydroxyl groups to the oxide bridge, attempts were made to oxidize 2b to the ketol 5. These experiments met with little success at first.[9] Acidic Cr(VI) reagents led to products arising from cleavage of the diol grouping. The main product (70%) was identified as the keto acid ester 6, which has been obtained more directly by Lemieux–Rudloff and RuO_4–$NaIO_4$ oxidation of 1b,[10] by exhaustive ozonolysis of 1b followed by oxidative work-up,[10] and by lead tetraacetate–Jones oxidation of 2b.[10] Two other compounds which were formed in variable amounts also resulted from cleavage of the diol system and contributed to an understanding of the path by which 6 was formed.

One of these had structure 7 on the basis of the empirical formula $C_{21}H_{30}O_6$ and spectral data. The infrared spectrum exhibited three carbonyl bands at 1790, 1732, and 1721 cm^{-1}, indicating the presence of strained lactone, ketone, and ester groups. The presence of a ketone was further verified by the CD curve. Since the nmr spectrum displayed no resonance below 2.6 ppm other than that of the methyl ester function, the only possible structure was 7. The stereochemistry of 7 was inferred from that subsequently deduced for the starting material 2b and was corroborated by the weak positive Cotton effect, which is in excellent agreement with the octant diagram (Figure 1).

The third product, $C_{21}H_{32}O_6$, isolated from the chromic acid oxidation of 2b, was also produced by reduction of 7 with sodium borohydride and could therefore be assigned formula 8a. Its nmr spectrum had a new broad multiplet at 3.80 ppm ($W_{1/2}$ = 20 Hz) which sharpened on addition of D_2O and appeared as a doublet of doublets (J = 10, 6 Hz) at 4.97 ppm in the nmr spectrum of 8b. Inspection of a model of 7 indicates that hydride attack should occur on the α face of the molecule and produce a β-oriented hydroxyl group. This is in accord with the nmr spectrum of 8b. The observed couplings (10, 6 Hz) fall within the ranges expected for axial–axial (8–13 Hz) and axial–equatorial (2–6 Hz) couplings for six-membered rings in the chair conformation.[11]

Chromic acid induced cleavages of vicinal secondary–tertiary diols have been reported previously,[12] although oxidation to a hydroxy ketone is usually the dominant reaction. In the case of 2b, however, inspection of the model shows that the two hydroxyl groups are ideally suited for formation of a cyclic chromate ester, the initial step in the path by which ditertiary 1,2-glycols are cleaved.[13,14]

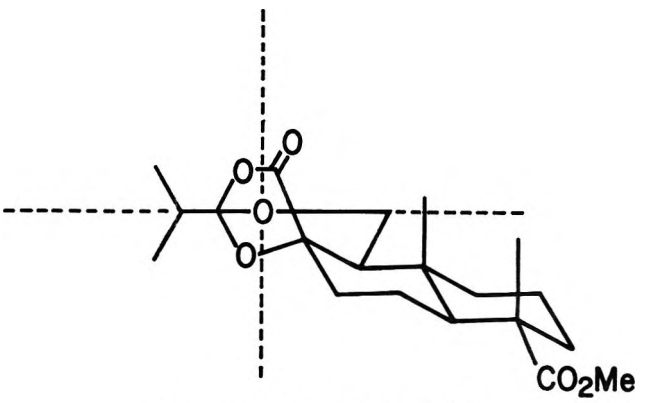
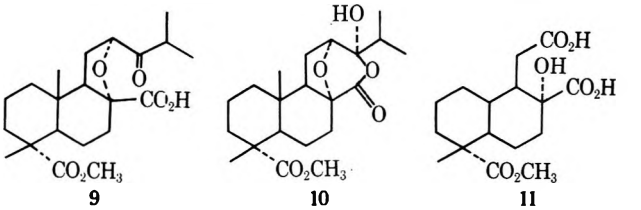


Figure 1.—Octant diagram of 7.



9 10 11

The desired ketol 5 was eventually prepared in low yield by the method of Walker,[12] which employs manganous ion to suppress the cleavage reaction. Subsequently the yield of 5 was improved by utilizing chromium trioxide–acetic anhydride in benzene.[15] The C-10 methyl resonance of 5 appeared at 0.71 ppm, a chemical shift similar to that of 4. Inspection of models showed that the C-10 methyl group is in the shielding cone of the carbonyl group at C-14 only if the oxide bridge is α oriented. The CD curve of the ketol exhibited a negative Cotton effect, which is in accord with the octant diagram (Figure 2).

Sodium borohydride reduction of 5 afforded a new diol 12[19] which must differ from 2b at C-14. This was confirmed by the infrared spectrum, which indicated a trans relationship of the two hydroxyl groups (two bands at 3420 and 3310 cm^{-1}, nonbonded and bonded hydroxyl). The C-10 methyl group, whose signal appeared at 0.93 ppm, was deshielded by 7 Hz in comparison with the C-10 methyl group of 2b. It follows[20] that the C-14 hydroxyl group of 12 is β and

(9) Oxidations which require removal of the proton at C-14 by a base in the initial step (Pfitzner–Moffat, Albright–Goldman, and modifications thereof) resulted in complete recovery of starting material. Inspection of molecular models indicates that, if the stereochemistry is as depicted in 2b, approach to H-14 by a base is severely restricted by the C-10 methyl group. Attempts to oxidize 2b with Sarett's or Collins' reagent also resulted in recovery of starting material. The reason for this is not readily apparent but may be due to an increase in the bulk of the oxidizing agent (association of two pyridine molecules with the chromium species) which inhibits formation of a chromate ester.

(10) (a) S. W. Pelletier, K. N. Iyer, C. W. Chang, and A. Ogiso, *Tetrahedron Lett.*, 3819 (1968); (b) S. W. Pelletier, K. N. Iyer, and C. W. Chang, *J. Org. Chem.*, **35**, 3535 (1970).

(11) L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Elmsford, N. Y., 1969, p 288.

(12) B. H. Walker, *J. Org. Chem.*, **32**, 1098 (1967).

(13) J. Rocek and F. H. Westheimer, *J. Amer. Chem. Soc.*, **84**, 2241 (1962).

(14) If this is so, the presumed intermediate 9 is formed *via* 4 rather than by cleavage of 5. Rearrangement of 5 to 8a, perhaps by way of the pseudo-acid 10, is followed by oxidation to 7. Further oxidation of 7 or its open-chain equivalent furnishes 11 and then 6.

(15) The success of these experiments leads to the conclusion that at least part of the cleavage of 2b to 6, 7, and 8a is due to the presence of Cr(IV), since the reactivity of this species is suppressed under these conditions.[12,16] That Cr(IV) is responsible for oxidative cleavage of secondary alcohols which contain a quaternary center has been demonstrated recently.[17,18]

(16) K. B. Wiberg and S. K. Mukherjer, *J. Amer. Chem. Soc.*, **93**, 2543 (1971).

(17) J. Rocek and A. E. Rudkowsky, *ibid.*, **90**, 2986 (1968).

(18) P. M. Nave and W. S. Trahanovsky, *ibid.*, **92**, 1120 (1970).

(19) The structure of a compound to which this formula was ascribed previously[5] has been revised.[7]

(20) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

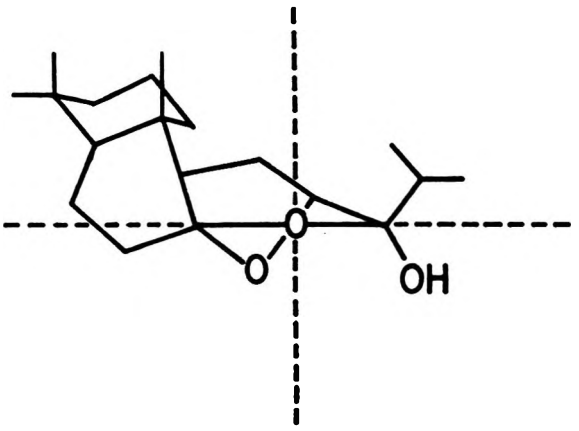


Figure 2.—Octant diagram of **5**.

that of **2b** is α. This is eminently reasonable, since inspection of models shows that hydride attack on **5** should occur exclusively from the α side. Therefore the stereochemistry of the permanganate oxidation product of levopimaric acid is correctly represented by **2a**.

Osmium Tetroxide Oxidation and Related Topics.—Marchand[8] reported that osmium tetroxide oxidation of **1b** in diethyl ether–pyridine furnished two dihydroxy esters which could be separated because the solubilities of their osmate ester–pyridine complexes differed. The major product, mp 138–140°, was assigned structure **13**; the minor product, mp 118–120°, formula **14**. Further oxidation of the major product yielded a tetraol formulated as **15**. No evidence was presented to substantiate these assignments.

Because recent work in our laboratory[1] led to the isolation and structure proof of **16**, whose melting point matched that of Marchand's major product, we repeated the osmium tetroxide oxidation of **1b** by the described method. The major product, mp 138–140° (70%), was indeed identical with **16**. The minor product, mp 112–114° (20%), was identified as **13**. A slightly broadened singlet at 5.27 ppm was characteristic of a vinyl proton at C-14, not C-12, and the presence of a multiplet at 3.87 ppm which sharpened on addition of D_2O confirmed that the secondary hydroxyl group was attached to C-12 rather than to C-14. The normal chemical shift of the C-10 methyl resonance (0.78 ppm) indicated α rather than β orientation of the two hydroxyl groups, in agreement with the rule that attack on the α face of levopimaric acid is generally preferred.

Osmylation of **1b** in anhydrous benzene furnished **16** and the tetraol **15**, mp 186–188°, which could also be prepared by further osmylation of **16**. The nmr spectrum of **15** indicated the presence of nine low-field protons, four of which disappeared after deuterium exchange. Of the remaining five, three could be assigned to the methyl ester function (singlet at 3.60 ppm), one to H-14 (singlet at 3.50 ppm), and one to H-12 (somewhat broadened triplet at 3.94 ppm).[21] Conclusive proof for the α orientation of the hydroxyl groups at C-12 and C-13 was provided by the observation that osmylation of **18**[23] and **19**,[7] both of authenticated stereochemistry, furnished **15**.[24,25]

Jones oxidation of **16** gave the ketol **21**, which could be obtained more directly from **2b** by the action of phosphoric acid in refluxing methanol, perhaps *via* β elimination of an intermediate **22**. Sodium borohydride reduction of **21** furnished **23** by attack from the less hindered α face. In accordance with the postulated stereochemistry, the C-10 methyl resonance was deshielded by 7 Hz in comparison with that of **21**.[20] Further confirmation for the orientation of the C-14 hydroxyl group was provided by the observation that **23** resisted acetylation with acetic anhydride–pyridine under conditions which afforded the 14-acetate **17** in quantitative yield. Models show that attack on the secondary hydroxyl group of **23** is severely hindered by the C-10 methyl and the axial hydrogen on C-6, while the secondary hydroxyl group of **16** is easily approached.

Osmylation of **23** gave the tetraol **24** by attack from the less hindered α side. This conclusion was supported by the appearance of the C-10 methyl resonance at 0.97 ppm. Use of Table I, which lists the approximate shielding constants for hydroxyl groups in ring C of 8α-abietanes and is derived from measurements on a number of compounds obtained in the course of our studies of resin acids, affords the same value.[27] Epoxidation of **23** yielded **25**, the stereochemistry of the oxirane being based on analogy to the osmium tetroxide oxidation and on the presence of a narrowly split triplet at 3.27 ppm (H-12). Attempts to cleave the epoxide ring with acid to form a new tetraol resulted in a complex mixture of at least seven components.

TABLE I

SUBSTITUENT SHIFTS FOR C-10 METHYL GROUP IN 8α-ABIETANES[a]

Substituent	J, Hz	Ppm
8α-OH	-5.0 ± 0.5	-0.08
12α-OH	-3.5	-0.06
12β-OH	3.0	0.05
13α-OH	-1.0	-0.02[b]
14α-OH	-3.5	-0.06
14β-OH	3.0	0.05

[a] From nmr spectra run at 60 MHz in $CDCl_3$ solution on at least three compounds. Reference compound is methyl 8α-abietan-18-oate. Positive values indicate shift toward lower field. [b] Two compounds.

The C-12 epimer **27** (H-14 singlet at 5.18, H-12 multiplet at 4.38 ppm) of **19** was formed by sodium borohydride reduction of **26**[23] and underwent spontaneous dehydration at room temperature to **28** (H-14 singlet at 5.64, H-7 multiplet at 5.43, H-12 multiplet at 4.30 ppm), presumably because this relieves the severe interaction between the pseudoaxial hydroxyl

(21) The appearance of this signal was compatible neither with an α-hydroxyl (H-12 β and axial) nor a β-hydroxyl (H-12 α and equatorial) group on C-12 and may reflect distortion of ring C as has been noted in similar compounds.[22]

(22) J. W. Huffman, T. Kamiya, L. H. Wright, J. J. Schmid, and W. Herz, *J. Org. Chem.*, **31**, 4128 (1966).

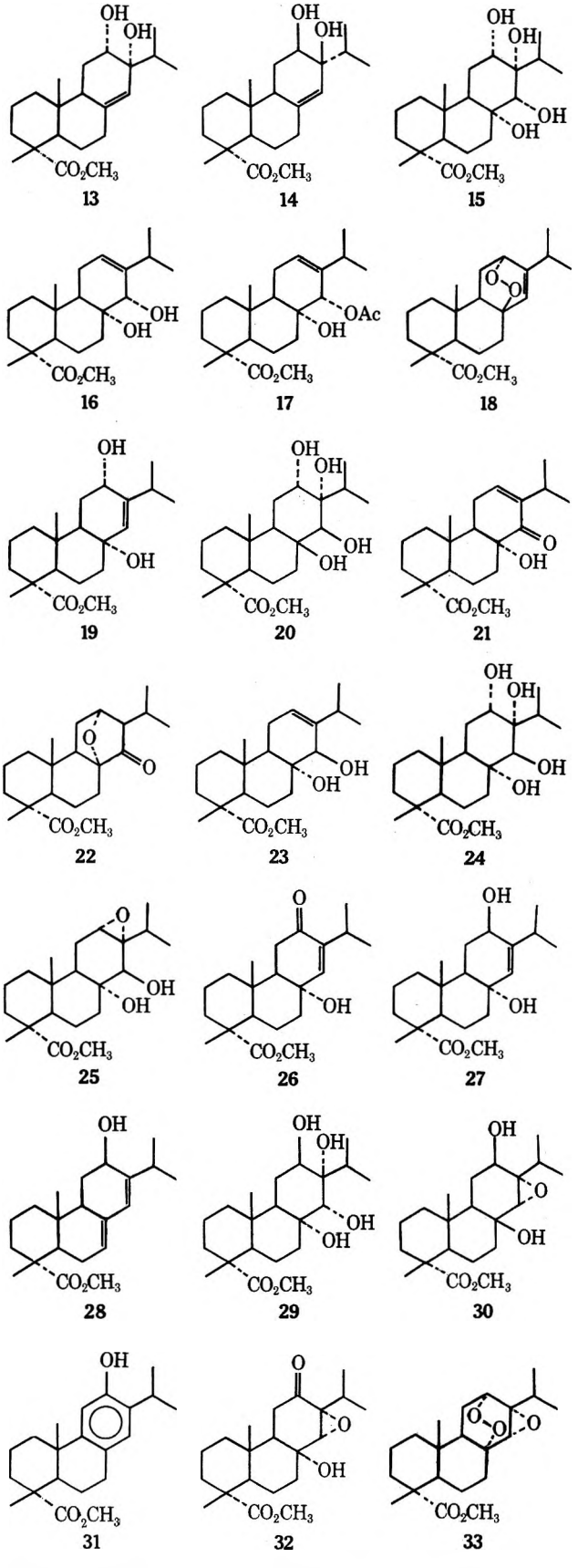
(23) R. N. Moore and R. V. Lawrence, *J. Amer. Chem. Soc.*, **80**, 1438 (1958); **81**, 458 (1959).

(24) Reductive cleavage of the transannular peroxide linkage of **18** was undoubtedly caused by the hydrogen sulfide used to cleave the osmate ester.

(25) Since it has been shown[26] that the double bond of $\Delta^{8(14)}$-abietanes is attacked from the β as well as the α face, it is reasonable to assume that the noncrystalline material obtained by Marchand[8] from the osmylation of the enediol, mp 118–120° (now shown to be **13**), was a mixture of **15** and **20**.

(26) J. W. Huffman, J. A. Alford, and R. R. Sobti, *J. Org. Chem.*, **35**, 473 (1970).

(27) Table I predicts a chemical shift of 0.86 ppm for the C-10 methyl signal of **17**. This is in good agreement with the observed value (0.88 ppm).

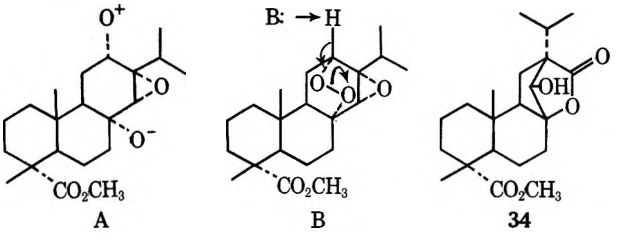


group at C-12 and the C-10 methyl group in **27**. Since **28** differs from methyl 12α-hydroxyabiet-7,13-dienoate,[28] the C-12 stereochemistry of **27** and **28** is as shown.

Osmylation of **27** produced a new tetraol **29** whose nmr spectrum displayed the C-10 methyl signal at anomalously high field (0.85 instead of 0.97 ppm as calculated from Table I). We ascribe this to a conformational change in ring C from a chair to a twist-boat, which minimizes the strong interaction between the C-10 methyl and the axial 12-hydroxyl group. An analogous interaction exists in **24** between the C-10 methyl and the 14-hydroxyl group, but here the interaction would be exacerbated rather than relieved by a conformational change.

Epoxidation of **19** furnished **30**, which had spectral properties in accord with the proposed stereochemistry and exhibited surprising stability toward aqueous acid when attempts were made to convert it to a tetraol. Elevated temperature caused quantitative conversion of **30** to methyl 12-hydroxydehydroabietate (**31**).[23] Oxidation of **30** with Collins' reagent afforded **32**, a substance also obtained quite surprisingly and more conveniently by refluxing **33**[7] in xylene.

The direct thermal conversion of **33** to **32** is difficult to explain in terms of the diradical mechanism discussed for the thermolysis of endoperoxides such as ascaridol,[29,30] but can be rationalized by assuming heterolytic cleavage of the peroxide bond to the zwitterion A, which suffers loss of a proton. This speculation is supported by the observation that substitution of the more polar solvent chlorobenzene for xylene produced a notable increase in the rate of conversion of **33** to **32**. The possibility that catalysis by the glass walls of the reaction vesse. might be responsible for the transformation of **33** to **32** through operation of the Kornblum–De La Mare mechanism B[31] was thought to be unlikely as addition of glass helices to increase the surface area did not result in an increased conversion rate. Moreover, it has been shown previously[7] that treatment with alkali transforms **33** into **34**, presumably *via* Favorskii rearrangement of the intermediate, not isolable **32** and subsequent lactonization; this conversion can also be catalyzed by weaker organic bases such as cyclohexylamine.



Experimental Section[32]

Methyl 8α(12α)-Oxido-13α,14α-dihydroxyabietan-18-oate (2b).—To a solution of 60 g of **1a** and 25 g of KOH in 1 l. of

(28) W. Herz, H. J. Wahlborg, W. D. Lloyd, W. H. Schuller, and G. W. Hedrick, *J. Org. Chem.*, **30**, 3190 (1965).

(29) J. Boche and O. Runquist, *ibid.*, **33**, 4285 (1968).

(30) K. K. Maheshwari, P. De Mayo, and D. Wiegand, *Can. J. Chem.*, **48**, 3265 (1970).

(31) N. Kornblum and P. De La Mare, *J. Amer. Chem. Soc.*, **73**, 880 (1951).

(32) Melting points are uncorrected. Analyses were carried out by Dr. F. Pascher, Bonn, Germany. Nmr spectra were run on Varian A-60 or Bruker HFX-90 instruments in deuteriochloroform with tetramethylsilane as internal standard, unless specified otherwise. Values for line positions are expressed in parts per million from the standard, coupling constants in hertz. Signals are characterized in the usual way: d, doublet; t, triplet; br, broadened singlet; m, multiplet; c, complex band whose center is given. Singlets are not marked. Ir spectra were run on a Perkin-Elmer Model 257 spectrometer as KBr pellets unless otherwise noted. ORD curves were recorded on a Jasco Model ORD/UV-5 recording spectropolarimeter in methanol solution; rotations were measured in 95% ethanol. Mass spectra were run at 70 MeV on a Nuclide 12 in medium resolution or a MS-902 high resolution mass spectrometer. Silica gel $PF_{254+366}$ (Merck) was used for preparative tlc.

water was added 90 g of $KMnO_4$ in small portions. The mixture was stirred for 1 hr in an ice bath and for 2 hr at room temperature. The MnO_2 formed was decomposed with $NaHSO_3$, the mixture was filtered, and the filtrate was acidified with dilute H_2SO_4. The product was taken up in ether, and the solution was extracted with saturated brine, dried, and partially concentrated *in vacuo*. The concentrated ether solution was methylated with diazomethane and chilled; this resulted in precipitation of **2b**. Further work-up of the mother liquors gave a total of 21.4 g (30%) of **2b**: mp 178–180°; nmr signals at 4.05 (br, sharpens on addition of D_2O, H-14), 3.64 (methoxyl), 3.30 (m, H-12), 1.12 (C-4 methyl), 1.06 (d) and 0.90 (d, J = 7.0 Hz, isopropyl), and 0.91 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35; O, 22.29. Found: C, 69.03; H, 9.41; O, 22.08.

The sulfite **3** was prepared by dissolving 0.5 g of **2b** in 4 ml of pyridine and adding 2 ml of thionyl chloride dropwise. After 10 min at room temperature, the mixture was poured into water and extracted with ether. The dried ether extracts were evaporated and the residue (**3**) was recrystallized from methanol: yield 0.475 g (85%); mp 153–155°; nmr signals at 5.04 (H-14), 3.68 (methoxyl), 3.32 (t, 3, H-12), 1.19 (C-4 methyl), 1.04 (d) and 1.01 (d, 7, isopropyl), and 0.81 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_6S$: C, 61.15; H, 7.82. Found: C, 61.31; H, 7.86.

Cleavage of 2b with Lead Tetraacetate.—A solution of 0.5 g of **2b** in the minimum amount of benzene was mixed with 0.62 g of lead tetraacetate in 25 ml of benzene, stirred for 1 hr, filtered, and concentrated *in vacuo*. The residue was taken up in ether, washed, dried, and evaporated, but could not be induced to crystallize. The product (**4**) was homogeneous on tlc and had nmr signals at 9.52 (-CHO), 3.65 (methoxyl), 3.28 (m, H-12), 1.15 (C-4 methyl), 0.95 (d) and 0.89 (d, J = 6.5, Hz, isopropyl), and 0.73 ppm (C-10 methyl).

Oxidation of 2b with Chromium Trioxide. A.—To a solution of 1 g of **2b** in 8 ml of acetic acid was added dropwise 0.8 g of CrO_3 in 4 ml of water and then 1 ml of sulfuric acid below 5°. The mixture was stirred for 2 hr, poured into water, and extracted with ether. The washed (bicarbonate, brine, and water) and dried ether extract gave 0.3 g of a gum. Preparative tlc resulted in isolation of two major components. The less polar material **7** was recrystallized from hexane: yield 175 mg (17%); mp 138.5–139.5°; ir 1794 (strained lactone), 1733 (ketone) and 1712, 1258 cm^{-1} (ester); nmr 3.66 (methoxyl), 1.23 (C-4 methyl), 1.00 (d, J = 7 Hz, 6 protons, isopropyl), and 1.01 ppm (C-10 methyl); ORD curve, $[\alpha]_{450}$ +18.1°, $[\alpha]_{320}$ 0°, $[\alpha]_{283}$ −197° (shoulder), $[\alpha]_{245}$ −341°, $[\alpha]_{227}$ 0° (last reading).

Anal. Calcd for $C_{21}H_{30}O_6$: C, 66.65; H, 7.99; O, 25.36. Found: C, 66.72; H, 8.01; O, 25.08.

The more polar substance **8a** was obtained after recrystallization from methanol in 90 mg (8%) yield: mp 174–176°; ir 3465, 1780, 1720, and 1250 cm^{-1}; nmr 3.80 (m, H-12), 3.65 (methoxyl), 1.22 (C-4 methyl), 1.01 (d) and 0.90 (d, J = 7 Hz, isopropyl), and 0.96 ppm (C-10 methyl). The same compound was obtained in 70 mg (70%) yield by $NaBH_4$ reduction of 100 mg of **7**.

Anal. Calcd for $C_{21}H_{32}O_6$: C, 66.29; H, 8.48; O, 25.23. Found: C, 66.31; H, 8.42; O, 25.18.

Acetylation of 0.2 g of **8a** with 3 ml of pyridine and 1 ml of acetic anhydride for 2 hr followed by the usual work-up gave **8b** as a gum which could not be induced to crystallize, but which was homogeneous on tlc.

The bicarbonate extract was acidified and extracted with ether. The usual work-up afforded an oily mixture, yield 0.64 g. Methylation with diazomethane and purification by chromatography gave a crystalline diester, mp 93–94°, yield 70%, which was identical in all respects with an authentic sample of the methyl ester of **6**.

B.—Tlc of the neutral fraction obtained by repetition of oxidation in the presence of 2 ml of a 50% solution of manganous nitrate indicated the presence of an additional component. Preparative tlc and recrystallization from methanol–water afforded 54 mg of **5**: mp 105–106°; ir 3420 (-OH), 1726 (ketone), 1712 and 1233 cm^{-1} (ester); nmr 3.68 (methoxyl), 3.59 m (H-12), 1.11 (C-4 methyl), 0.98 (d) and 0.94 (d, J = 7 Hz, isopropyl), and 0.71 ppm (C-10 methyl); ORD curve, $[\alpha]_{450}$ −22.5°, $[\alpha]_{345}$ −156°, $[\alpha]_{322}$ 0°, $[\alpha]_{293}$ +198°, $[\alpha]_{250}$ +128° (last reading).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.55; O, 21.97, mol wt, 364.2249. Found: C, 68.68; H, 8.77; O, 22.22; mol wt (mass spectrometry), 364.2277.

C.—To a solution of 0.8 g of CrO_3 in 20 ml of acetic anhydride was added 1 g of **2b** in 10 ml of dry benzene. The mixture was stirred at room temperature for 3 hr, poured into water, and extracted with ether. The washed and dried ether extracts were evaporated and subjected to preparative tlc, yield 270 mg (27%) of 4 and 310 mg (31%) of **5**.

Sodium Borohydride Reduction of 5.—A solution of 0.3 g of **5** in methanol was reduced with excess $NaBH_4$. The usual work-up gave, after recrystallization from methanol–water, 0.22 g (73%) of **12**: mp 162–163°; ir 3420, 3315 (-OH), 1722, and 1242 cm^{-1} (ester); nmr 4.73 (d br, J = 5 Hz, H-14, collapses on addition of D_2O), 3.63 (methoxyl), 3.36 (t, J = 2.5 Hz, H-12), 3.11 (d, J = 5 Hz, OH), 1.2 (C-4 methyl), 1.02 (d) and 0.90 (d, J = 7 Hz, isopropyl), and 0.93 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35; O, 21.83. Found: C, 68.77; H, 9.42; O, 22.16.

Osmium Tetroxide Oxidation of 1b. A.—A solution of 1.4 g of **1b** in 50 ml of anhydrous benzene was oxidized with 1 g of OsO_4 for 3 days. Methanol was added and H_2S was bubbled through the solution for 1 hr. The mixture was filtered and evaporated and the residual gum was chromatographed over silica gel. The less polar material (**16**) was recrystallized from methanol, yield 0.3 g (19%), mp 138–140°. The substance was identical in all respects with **16** described in our earlier publication.[1] The more polar material (**15**) was recrystallized from hexane–ether: yield 0.17 g (10%); mp 186–188°; ir 3400 (strong) and 1722 cm^{-1}; nmr (DMSO-d_6) 3.94 (m, H-12, collapses to t br, J = 6.5 Hz, on addition of D_2O), 3.50 (m, H-14, collapses to singlet on D_2O exchange), 1.10 (C-4 methyl), 0.93 (d, J = 7 Hz, 6 protons, isopropyl), 0.86 ppm (C-10 methyl), and four -OH multiplets.

Anal. Calcd for $C_{21}H_{36}O_6$: C, 65.60; H, 9.44; O, 24.97. Found: C, 66.02; H, 9.14; O, 24.88.

B.—Oxidation of 2.5 g of **1b** by the procedure of Marchand[8] gave, by decomposition of the ether-soluble osmate, 2.1 g (76%) of **16**. Decomposition of the ether-insoluble osmate and recrystallization from methanol–water afforded 0.6 g (21%) of **13**: mp 112–114°; nmr 5.27 (br, H-14), 3.87 (m, H-12), 3.60 (methoxyl), 1.26 (C-4 methyl), 0.91 (d, J = 6.5 Hz, 6 protons, isopropyl), and 0.78 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78; O, 18.26. Found: C, 71.97; H, 9.94; O, 17.88.

Acetylation of 0.2 g of **16** in 3 ml of pyridine with 1 ml of acetic anhydride for 1 hr at room temperature followed by the usual work-up gave 0.175 g of **17**, which was recrystallized from hexane: mp 140–141°; nmr 5.77 (br, H-14), 5.60 (m, H-12), 3.61 (methoxyl), 2.13 (acetate), 1.15 (C-4 methyl), 1.01 (d, J = 7 Hz, 6 protons, isopropyl), and 0.88 ppm (C-10 methyl). Under these conditions, **23** was not acetylated and was recovered in quantitative yield.

Osmium Tetroxide Oxidation of 19.—A solution of 1.3 g of **19**[7] in 150 ml of anhydrous benzene was oxidized with 1 g of osmium tetroxide in 20 ml of benzene as described for **1b**. The organic product was recrystallized from hexane–ether, yield 0.43 g (30%), mp 186–188°, identical with **15** prepared from **1b**.

Preparation of 21.—A solution of 0.5 g of **2b** in 100 ml of methanol and 10 ml of 85% phosphoric acid was refluxed overnight, poured into water, and extracted with ether. The washed and dried ether extract yielded 0.2 g (42%) of **21**: mp 159.5–160° after recrystallization from hexane; ir 1728 and 1241 (ester) and 1668 cm^{-1} (unsaturated ketone); nmr 6.59 (t, J = 3.5 Hz, H-12), 3.69 (methoxyl), 2.20 (-OH, disappears on D_2O exchange), 1.10 (C-4 methyl), 1.04 (d) and 1.00 (d, J = 7 Hz, isopropyl), and 0.69 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26; O, 18.36. Found: C, 72.19; H, 9.30; O, 18.50.

$NaBH_4$ Reduction of 21.—A solution of 1.5 g of **21** in methanol was reduced with excess $NaBH_4$. When tlc indicated that starting material had been consumed, the solvent was removed at reduced pressure. The residue was extracted several times with hot benzene and the undissolved material (**23**) was recrystallized from hexane: yield 1.29 g (86%); mp 124–126°; ir 3445 (strong) and 1724 cm^{-1} (ester); nmr 5.56 (t, J = 5 Hz, H-12), 3.77 (m, H-14, sharpens on addition of D_2O), 3.60 (methoxyl), 1.12 (C-4 methyl), 1.06 (d) and 1.02 (d, J = 7 Hz, isopropyl), and 0.89 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78; O, 18.26. Found: C, 71.78; H, 9.75; O, 18.28.

Osmium Tetroxide Oxidation of 23.—Osmylation of 1.0 g of **23** in anhydrous ether with 1 g of OsO_4 for 24 hr, followed by concentration at reduced pressure, dilution with methanol, decomposition with hydrogen sulfide, and work-up in the usual manner, gave a gum. Recrystallization from hexane–ether afforded 0.21 g (19%) of **24**: mp 197–199°; ir 3415 (strong) and 1725 cm^{-1}; nmr (DMSO-d_6) 3.85 (q, J = 5 Hz, H-12, collapses to t on D_2O exchange), 3.58 (methoxyl), 1.16 (C-4 methyl), 0.96 (d, J = 7 Hz, 6 protons, isopropyl), 0.97 ppm (C-10 methyl), and four OH multiplets.

Anal. Calcd for $C_{21}H_{36}O_6$: C, 65.60; H, 9.44; O, 24.97. Found: C, 65.44; H, 9.25; O, 24.92.

Epoxidation of 23.—A solution of 0.5 g of **23** was allowed to stand with 0.35 g of *m*-chloroperbenzoic acid at room temperature overnight and extracted with sodium bicarbonate solution, water, and saturated brine. The dried organic layer was evaporated and the residue was recrystallized from hexane: yield of **25** 0.32 g (61%); mp 156–158°; ir 3325 (strong) and 1724 cm^{-1}; nmr 3.66 (br, H-14, sharpens on addition of D_2O), 3.58 (methoxyl), 3.27 (t br, J = 2 Hz, H-12), 1.17 (C-4 methyl), 1.00 (d) and 0.88 (d, J = 7 Hz, isopropyl), and 0.90 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.86; H, 9.35; O, 21.83. Found: C, 69.20; H, 9.39; O, 21.68.

$NaBH_4$ Reduction of 26.—Reduction of 5 g of **26**[23] with $NaBH_4$ in the manner described for **21** gave, in the hot benzene extracts, a gum which was recrystallized from hexane: yield of **27** 2.65 g (52%); mp 143.5–145°; ir 3458 (strong) and 1705 cm^{-1}; nmr 5.18 (H-14), 4.37 (m, H-12, sharpens on addition of D_2O), 3.60 (methoxyl), 1.17 (C-4 methyl), 1.03 d (J = 7 Hz, 6 protons, isopropyl), and 0.80 ppm (C-10 methyl). This material was converted to **28** on standing in chloroform solution.

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78; O, 18.26. Found: C, 72.24; H, 9.71; O, 18.15.

Evaporation of the mother liquors of **27** produced a gum which was homogeneous (tlc) but could not be induced to crystallize and was identified as **28** spectroscopically. Its nmr spectrum exhibited signals at 5.64 (H-14), 5.33 (m, H-7), 4.30 (m, H-12, sharpens on addition of D_2O), 3.59 (methoxyl), 2.60 (m, –OH), 1.27 (C-4 methyl), 1.03 (d, J = 7 Hz, 6 protons, isopropyl), and 0.80 ppm (C-10 methyl).

Osmium Tetroxide Oxidation of 27.—Osmylation of 1 g of **27** with 1 g of OsO_4 in anhydrous ether and work-up as described for **23** gave **29** which was recrystallized from hexane–ether: yield 0.23 g (21%); mp 220–222°; ir 3425 (strong) and 1710 cm^{-1}; nmr (DMSO-d_6) 4.1 (t br, 8, H-12), 3.60 (methoxyl, superimposed on H-14), 1.20 (C-4 methyl), 0.93 (d) and 0.88 (d, J = 7 Hz, isopropyl), 0.85 ppm (C-10 methyl), and four OH multiplets.

Anal. Calcd for $C_{21}H_{36}O_6$: C, 65.60; H, 9.44; O, 24.97. Found: C, 65.72; H, 9.16; O, 25.10.

Epoxidation of 19.—Oxidation of 1 g of **19**[7] with 0.7 g of *m*-chloroperbenzoic acid in chloroform at room temperature for 3 hr and work-up as described for **23** gave, after recrystallization from hexane, 0.55 g (52%) of **30**: mp 145–147°; ir 3478, 1705, and 1164 cm^{-1}; nmr 4.28 (t br, J = 6 Hz, H-12, sharpens on addition of D_2O), 3.66 (methoxyl), 3.02 (H-14), 1.23 (C-4 methyl), 1.04 (C-10 methyl) and 0.98 (d, J = 7 Hz, isopropyl), and 0.88 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35; O, 21.83. Found: C, 68.68; H, 9.45; O, 22.08.

Reaction of 30 With Acid.—A solution of 0.5 g of **30** in 50 ml of tetrahydrofuran and 50 ml of 20% perchloric acid was stirred at room temperature for 2 days. Since tlc examination revealed that only starting material was present, the solution was refluxed on the steam bath for 3 hr, cooled, poured into water, and extracted with ether. The washed and dried ether extract was evaporated. The residual gum solidified on trituration with hexane, yield 60%, mp 156–158°, identified as methyl 12-hydroxydehydroabietate (**31**) by comparison with an authentic sample.[23] The ether mother liquors yielded an additional 30% of **31**.

Preparation of 32. A.—Oxidation of 0.5 g of **30** with Collins' reagent by the procedure of Ratcliffe and Rodehorst[33] and recrystallization of the crude product from hexane gave 0.32 g (64%) of **32**: mp 83–85°; ir 3478, 1728, 1709, and 1245 cm^{-1}; nmr 3.63 (methoxyl), 3.31 (H-14), 1.18 (C-4 methyl), 1.00 (d) and 0.96 (d, J = 7 Hz, isopropyl), and 0.85 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95. Found: C, 68.86; H, 8.86; O, 22.09.

B.—A solution of 1 g of **33**[7] in 50 ml of *p*-xylene was refluxed for 20 hr and evaporated at reduced pressure. The residue was taken up in hot hexane and allowed to cool, whereupon crude **32** precipitated. The mother liquors were evaporated, chromatographed over a short alumina column, and evaporated to furnish additional crude **32**. Recrystallization from hexane afforded 0.71 g (71%) of **32**, mp 83–85°.

Rearrangement reactions were run simultaneously on 0.1 g of **33** in 15 ml of xylene, 15 ml of xylene packed with glass beads, and 15 ml of chlorobenzene, the progress of the reaction being followed by tlc. After 4 hr, conversion of **33** to **32** in chlorobenzene was complete, whereas the xylene runs were just beginning to show a detectable amount of **32**.

A solution of 1 g of **33** in 20 ml of cyclohexylamine was refluxed for 3 hr, poured into dilute phosphoric acid, and extracted with ether. The usual work-up and recrystallization from methanol–water afforded 0.85 g (85%) of pure **34**,[7] mp 241–243°.

Registry No.—**1a**, 79-54-9; **1b**, 3513-69-7; **2b**, 34226-16-9; **3**, 34202-06-7; **4**, 34226-17-0; **5**, 34226-18-1; **7**, 34226-19-2; **8a**, 34217-09-9; **12**, 34217-10-2; **13**, 34217-11-3; **15**, 34217-12-4; **21**, 32111-53-8; **23**, 34217-14-6; **24**, 34217-15-7; **25**, 34217-16-8; **27**, 34217-17-9; **28**, 34217-18-0; **29**, 34217-19-1; **30**, 34217-20-4; **32**, 34217-21-5; potassium permanganate, 7722-64-7; osmium tetroxide, 20816-12-0.

(33) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).

Molecular Rotations of Steroids in Relation to Their Structures. The *S* value of a Hydrogen Atom and That of a Hydroxyl Radical

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S values of the hydrogen atom and of the hydroxyl radical vary discontinuously over a range. The particular *S* value selected from a small set of discrete values depends on influences in the remainder of the molecule which can be transmitted through a coplanar zigzag chain.

Though optical rotatory dispersion and optical circular dichroism of steroids have been investigated actively for about two decades,[1,2] many reports of molecular rotations [M]D of steroids measured at the sodium D line date from earlier periods. Therefore, it is necessary to arrange them and to try to explain (or interpret) them in the framework of a physical theory.

In 1959, Brewster applied his idea of a screw pattern

(1) C. Djerassi, "Optical Rotatory Dispersion, Applications to Organic Chemistry," McGraw-Hill, New York, N. Y., 1960.

(2) For example, see A. I. Scott and A. D. Wrixon, *Tetrahedron*, **27**, 2339 (1971).

TABLE I

[M]^{20}D (IN CHLOROFORM) OF STEROID DERIVATIVES

Compd	Position and orientation of X	[M]^{20}D for X: H	F	(OH)	Cl	Br	I	Figure
		5α-Cholestane derivative						
1	2	221.2*	*mm*	*mm*	188.6*	173.4*	*mm*	10
2	2α	435.0*	*mm*	418.8[a,*]	*mm*	414.4[a,*]	*mm*	5
2′	2β	435.0*	*mm*	165.1[a,*]	*mm*	−223.5[a]	*mm*	5
3	2α	164.3	242.8[b,*]	153.0	213.1[c]	190.0	154.8[c]	*tt*[uu]
3′	2β	164.3	*mm*	*mm*	522.2	758.9[d]	*mm*	11
4	2α	522.2	*mm*	*mm*	519.3[e,*]	463.0[e,*]	*mm*	11
4″	2β	219.0*	*mm*	*mm*	551.2*	710.0[e,*]	*mm*	10
5	2α	338.5	*mm*	*mm*	360.4[f,*]	435.7[f,*]	*mm*	7
6	2α	−30.8	*mm*	*mm*	−21.0[f,*]	2.3[f,*]	*mm*	11
6′	2β	−30.8	*mm*	*mm*	410.7[f,*]	533.1[f,*]	*mm*	10
7	2α	89.4*	*mm*	72.8[g]	63.5	56.1	*mm*	5
7″	2β	97.2*	*mm*	133.5[g]	165.0	205.7	272.7[h]	6
8	2α	56.0	*mm*	*mm*	20.9*	−40.8	*mm*	11
8″	2β	120.6[i]	*mm*	188.5[j]	297.7[h]	361.8	506.5[h]	4
9′	2β	124.2	*mm*	224.3	273.8	323.2	*mm*	5
10′	2β	129.6*	*mm*	289.9	298.9	413.8	*mm*	7
11	3α	104.4[k]	125.0[l]	97.2*	124.2	129.6*	161.0[m]	3
11′	3β	104.4[k]	85.9[l]	89.4*	109.9	*mm*	156.6[n,*]	3
12′	3β	44.5[o]	*mm*	212.3	405.1[p]	*mm*	*mm*	6
13	3α	193.3	*mm*	*mm*	673.8	856.6	*mm*	10
14	3α	130.2	*mm*	137.6[q]	224.3	289.9	*mm*	3
15	3α	116.3	*mm*	145.6	290.7	366.9	512.1[r]	8
15″	3β	−4.3	*mm*	*mm*	−130.2[h]	−112.1[h]	−105.8[h]	*tt*[uu]
16	3α	*mm*	*mm*	165.0	273.8	298.9	*mm*	12
16″	3β	*mm*	*mm*	63.5	−28.7	−75.3[s]	*mm*	12
17	3α	*mm*	*mm*	205.7	323.2	413.8	*mm*	13
17″	3β	*mm*	*mm*	56.1	−82.6[s]	−153.8[s]	*mm*	12
18	3α	244.6[o]	*mm*	444.7[k]	684.6[t,*]	*mm*	*mm*	6
18′	3β	244.6[o]	*mm*	172.1*	105.3[t,*]	*mm*	*mm*	6
19	3α	−200.2	*mm*	−170.1*	−12.2	−22.5	*mm*	*tt*[vv]
19′	3β	−200.2	−176.8[u]	−150.8	−107.4	−98.8	−62.1	5
20′	3β	−468.2	*mm*	−446.2	−401.1	−387.1	*mm*	4
21′	3β	*mm*	*mm*	−210.5	−190.1	*mm*	−140.1*	12
22	3α	*mm*	*mm*	10.1*	32.4*	46.6	*mm*	12
22′	3β	*mm*	*mm*	−20.1	−4.2*	14.0	41.0	13
23′	3β	31.1	*mm*	52.6*	61.4	65.5	77.2	5
24	4	338.5	374.5[v]	319.3*	444.2[w]	496.0[w]	*mm*	3
25	5α	164.3	145.7[x]	165.1	*mm*	23.3[y]	*mm*	3
26	5α	*mm*	*mm*	13.1*	−123.0	−225.0*	*mm*	12
27	5α	52.6*	54.9[z]	12.6[pp]	−96.6	−183.8	*mm*	6
28	5α	*mm*	*mm*	−39.5	−123.5	−226.0	*mm*	13
29	5α	*mm*	*mm*	−149.2	−144.9	−233.9*	*mm*	7
30	5α	*mm*	*mm*	−108.6	−126.4	−190.9	*mm*	7
31	5α	109.9	*mm*	103.7[aa]	53.9[qq]	16.5*	*mm*	3
32	5α	114.1	*mm*	*mm*	442.2[bb]	307.3[bb]	*mm*	*tt*[uu]
33	5α	*mm*	*mm*	−179.2[pp,*]	−429.5[cc]	−675.1[cc]	*mm*	13
34	6α	104.4[k]	*mm*	136.0*	187.3[dd]	225.8[dd]	*mm*	4
34′	6β	104.4[k]	*mm*	*mm*	8.1[ee]	−72.3[ee]	*mm*	11
35	6α	338.5	410.7[ff]	325.7*	247.3	245.7	*mm*	*tt*[vv]
35′	6β	338.5	40.3[ff]	107.0*	62.9	27.8	*mm*	13
36′	6β	165.1	277.6[gg]	*mm*	13.1*	−65.0[y]	*mm*	11
37′	6β	11.7[hh]	*mm*	−177.7*	−233.9*	−270.7	*mm*	13
38′	6β	*mm*	*mm*	−129.3	−190.9	−260.2*	*mm*	13
39′	6β	38.9	*mm*	*mm*	−25.4[cc]	−51.4[cc]	*mm*	10
40	6α	−181.7*	−72.8[ii]	*mm*	−33.7[ii]	−32.6[ii]	5.1[ii]	*tt*[uu]
40′	6β	−181.7*	−323.7[ii]	*mm*	139.0[ii]	316.6[ii]	584.3[ii]	8
41	7α	93.2	*mm*	42.8	−85.5	−90.3	*mm*	*tt*[vv]
42	7α	−184.3	*mm*	−389.1	−764.2	−1233.5	−2024.3	6
43	7α	−73.6	*mm*	−253.4	−632.9	−1025.4	−1665.0*	6
43′	7β	−73.6	*mm*	65.9	318.8	113.9[oo]	*mm*	6
44	7α	−107.4	*mm*	*mm*	−725.3*	−1135.0*	*mm*	11
45′	(3β)′[ee]	417.2	*mm*	*mm*	449.4*	*mm*	401.4*	*tt*[vv]
46′	(3β)′	263.6	*mm*	*mm*	288.5	*mm*	315.6*	*tt*[vv]
47′	(3β)′	−184.3	*mm*	*mm*	−178.8	−143.1	135.3	11
48′	(6β)′	−237.2*	*mm*	*mm*	−235.1*	*mm*	−209.4*	*tt*[vv]

TABLE I
(*Continued*)

Compd	Position and orientation of X	[M]^{20}D for X: H	F	(OH)	Cl	Br	I	Figure
		5β-Cholestane (*i.e.*, coprostane) derivative						
49	3α	96.9	*mm*	120.5	134.4[ii]	149.0[ii]	*mm*	5
49′	3β	96.9	*mm*	93.3	91.6*	81.3	*mm*	6
50′	(3β)′	411.3[kk,*]	*mm*	*mm*	440.4*	*mm*	435.6*	*tt*[vv]
		Androstane derivative						
51	2α	238.7*	*mm*	*mm*	352.3	324.2*	375.9	10
52	17α	299.7*	319.5[l]	206.2[pp,*]	135.0[l]	63.2[l]	*mm*	6
		Pregnane derivative						
53	9α	861.3*	*mm*	*mm*	1101.1*	1131.3*	*mm*	10
54	9α	610.8[nn,*]	638.0[ll]	*mm*	610.1*	642.9	769.1*	11
		Spirostane derivative						
55	12α	−223.1	*mm*	*mm*	*mm*	−149.5*	−90.1*	11
		Cholaoic acid derivative						
56	12α	178.8[rr]	*mm*	396.5[rr]	634.6	981.7	*mm*	6
57	12α	245.5[rr]	*mm*	500.2[rr]	716.2	*mm*	*mm*	8

Compd	Steroid
1	2-X-(5α)cholest-1-en-3-one
2′	2β-X-(5α)cholestan-1-one
3′	2β-X-(5α)cholestan-3-one
4″	2β-X-2α-chloro-(5α)cholestan-3-one
6	2α-X-(5α)cholest-5-en-3-one
7	2α-X-(5α)cholestan-3β-ol
8	2α-X-(5α)cholestan-3β-yl acetate
9′	2β-X-3α-chloro-(5α)cholestane
11	3α-X-(5α)cholestane
12′	3β-X-(5α)cholest-1-ene
14	3α-X-(5α)cholestan-2β-ol
15″	3β-X-(5α)cholestan-2α-yl acetate
16″	3β-X-2α-chloro-(5α)cholestane
17″	3β-X-2α-bromo-(5α)cholestane
18′	3β-X-(5α)cholest-4-ene
19′	3β-X-(5α)cholest-5-ene
21′	3β-X-24-ethyl-(5α)cholest-5,22-diene
22′	3β-X-(5α)cholestan-6-one
24	4-X-(5α)cholest-4-en-3-one
26	5-X-6β-chloro-(5α)cholestan-3-one
28	5-X-6β-chloro-(5α)cholestan-3β-ol
30	5-X-6β-chloro-(5α)cholestan-3β-yl benzoate
32	5-X-(5α)cholestan-4-one
34	6α-X-(5α)cholestane
35	6α-X-(5α)cholest-4-en-3-one
36′	6β-X-(5α)cholestan-5-ol-3-one
38′	6β-X-5-bromo-(5α)cholestan-3β-yl benzoate
40	6α-X-(5α)cholestan-7-one
41	7α-X-(5α)cholestane
43	7α-X-cholest-5-en-3β-yl benzoate
44	7α-X-3β-chloro-cholest-5-ene
46′	3β-(X-acetoxy)-4,4,14α-trimethyl-(5α)cholest-8-ene
48′	6β-(X-acetoxy)-(5α)cholestan-5-ol-3β-yl acetate
49′	3β-X-(5β)cholestane
51	2α-X-17β-methoxycarbonyl-(5α)androstan-3-one
53	9α-X-pregn-4-en-17α-ol-3,11,20-trion-21-yl acetate
55	12α-X-(5α,22a)spirostan-11β-ol-3β-yl acetate
57	methyl ester of 12α-X-3α-acetoxy-(5β)chol-9(11)-en-24-oic acid

Compd	Steroid
2	2α-X-(5α)cholestan-1-one
3	2α-X-(5α)cholestan-3-one
4	2α-X-2β-chloro-(5α)cholestan-3-one
5	2α-X-(5α)cholest-4-en-3-one
6′	2β-X-(5α)cholest-5-en-3-one
7″	2β-X-(5α)cholestan-3α-ol
8″	2β-X-(5α)cholestan-3α-yl acetate
10′	2β-X-3α-bromo-(5α)cholestane
11′	3β-X-(5α)cholestane
13	3α-X-(5α)cholestan-2-one
15	3α-X-(5α)cholestan-2β-yl acetate
16	3α-X-2β-chloro-(5α)cholestane
17	3α-X-2β-bromo-(5α)cholestane
18	3α-X-(5α)cholest-4-ene
19	3α-X-(5α)cholest-5-ene
20′	3β-X-(5α)cholest-5,7-diene
22	3α-X-(5α)cholestan-6-one
23′	3β-X-(5α)cholestan-6β-ol
25	5-X-(5α)cholestan-3-one
27	5-X-(5α)cholestane-3β,6β-diol
29	5-X-6β-chloro-(5α)cholestan-3β-yl acetate
31	5-X-3β-chloro-(5α)cholestane
33	5-X-(5α)cholestan-6-one
34′	6β-X-(5α)cholestane
35′	6β-X-(5α)cholest-4-en-3-one
37′	6β-X-5-bromo-(5α)cholestan-3β-yl acetate
39′	6β-X-(5α)cholestan-5-ol
40′	6β-X-(5α)cholestan-7-one
42	7α-X-cholest-5-en-3β-yl acetate
43′	7β-X-cholest-5-en-3β-yl benzoate
45′	3β-(X-acetoxy)-4,4,14α-trimethyl-(5α)cholest-7,9(11)-diene
47′	3β-(X-acetoxy)cholest-5-ene
49	3α-X-(5β)cholestane
50′	3β-(X-acetoxy)-5-methyl-19-nor-(5β)cholest-9-en-6β-yl acetate
52	17α-X-androst-4-en-3-one
54	9α-X-pregn-4-ene-11β,17α-diol-3,20-dion-21-yl acetate
56	methyl ester of 12α-X-(5β)chol-9(11)-ene-3α-ol-24-oic acid

Unless noted otherwise, [M]^{20}D were calculated from [α]D, cited by J. P. Mathieu and A. Petit, in "Tables de Constantes et Données Numériques. 6. Constantes Sélectionnées. Pourvoir Rotatoire Naturel. I. Stéroïdes," Masson et Cie, Paris, 1956. See page 1408 for footnotes.

TABLE I (*Continued*)

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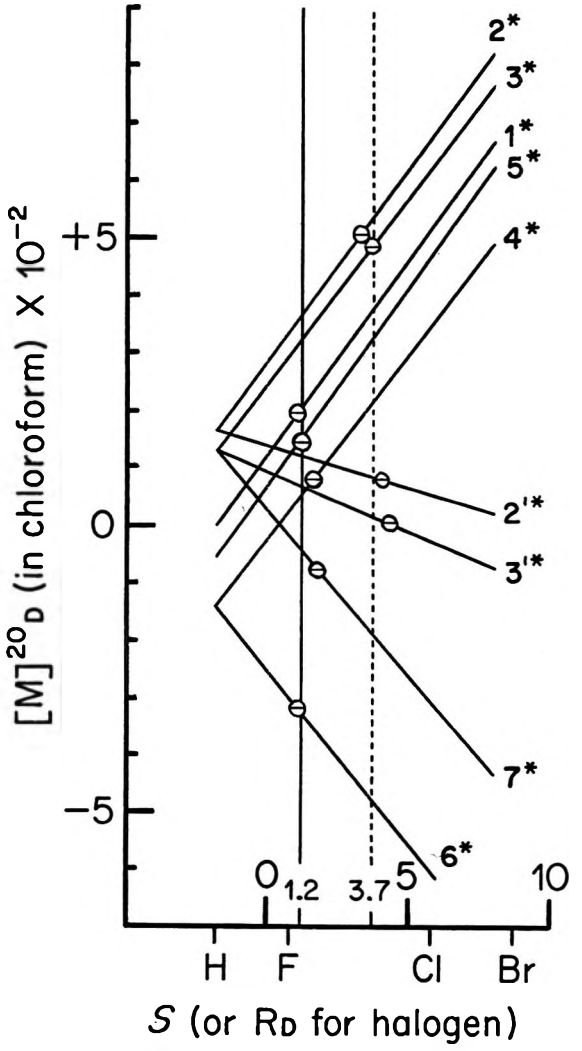

Figure 1.—Estimation of the S value of a radical OH which is attached to the C-1 atom in a pyranose ring;[10,11] ⊖, OH.

of electron polarizability to calculating the [M]D values of steroids, but some of his calculated values deviate considerably from the observed values.[3]

(3) J. H. Brewster, *J. Amer. Chem. Soc.*, **81**, 5475, 5483, 5493 (1959).

The present author recently found[4] some empirical rules graphically which govern the molecular rotations $[M]^{20}D$ (at 20°) of poly-*O*-acetyl (or benzoyl) glycopyranosyl compounds, RX. These rules[5] can be summarized by eq 1 where a and b are constants inherent in

$$[M]^{20}D \text{ value of a compound, RX} = a + bS \qquad (1)$$

the moiety, R, and S is a new coefficient which is concerned with some optical properties of the atom (or radical) X. It was found that the S value of a halogen atom is equal to its atomic refraction, R_D, but the S value of a hydrogen atom is -1.8.[5] The following method was proposed[6] in order to estimate the S value of an OH radical in a compound, ROH.

First, a straight $[M]^{20}D$ *vs.* S line is drawn for a series of compounds RX (where X is H, F, Cl, Br, or I).[7] Next, a horizontal line is drawn whose ordinate is $[M]^{20}D$ of ROH (eq 2).

$$\text{ordinate value} = [M]^{20}D \text{ value of ROH} \qquad (2)$$

If the OH radical has its own S value, the abscissa at the intersection of these two lines (*i.e.*, the standard line of RX and the horizontal line of ROH) should be the S value of the OH radical which is combined with the R moiety, because $[M]^{20}D$ of ROH should fall on both of the two lines at this abscissal value.[8]

By using the ITL method[8] in Figure 1 of the previous paper,[6] the S value of the OH radical in poly-*O*-acetylglycopyranosyl compounds was estimated as 1.2. This value has been proved to be applicable not

(4) S. Yamana, *J. Org. Chem.*, **31**, 3698 (1966).

(5) Rule 1. When the molecular rotation of poly-*O*-acetyl- or benzoylglycopyranosyl halides RX, where X is F, Cl, Br, or I, is plotted against the atomic refraction of X, straight lines are obtained, regardless of the configuration at the 1 position. Rule 2. An abscissal value can be found for hydrogen so that the "hydrides," RH, also fall on the lines mentioned in rule 1. Rule 3. The abscissal value of the point for the "hydride" is −1.8 (by the R_D scale for halogen) and is not related to the atomic refraction of hydrogen, 1.028.

(6) S. Yamana, *J. Org. Chem.*, **33**, 185 (1968).

(7) This straight $[M]^{20}D$ *vs.* S line is called the "Standard Line" of this series of compounds RX.

(8) This method of estimating the S value of an atom or radical in an optically active molecule will be called the "Intersecting Two Lines (or ITL) method," hereafter.

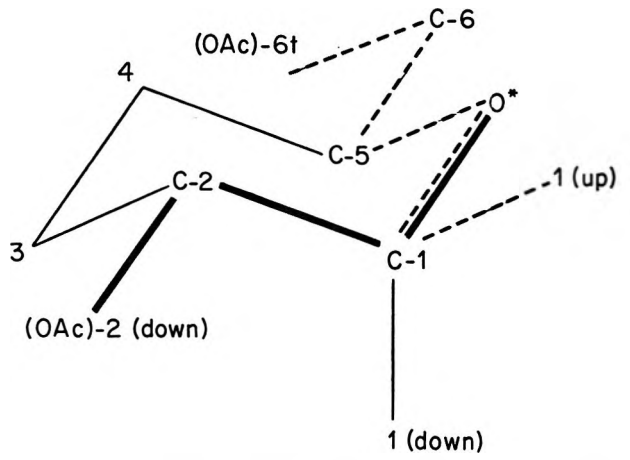

Figure 2.—Two coplanar zigzag chains, containing the C-1 atom of a pyranose ring.

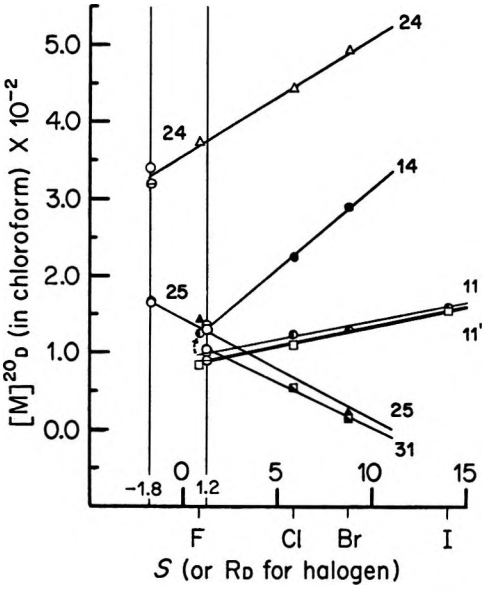

Figure 3.—Estimations of the S value of H and OH in steroid derivatives:[17,20,21] A 1 class (S of H = S of OH = −1.8); B 1 class (S of H = S of OH = 1.2). O, H; ⊖, OH.

only to all nonsubstituted glycopyranosyl compounds[6] but also to 6-Y-6-deoxy-D-glucopyranose derivatives.[9]

In order to reexamine the S value of the OH radical, the earlier figure is reproduced (with some changes) as Figure 1[10,11] of the present paper.

Figure 1 shows that the abscissal value of the OH radical is *ca.* 1.2 in some compounds (*i.e.*, **1***, **4***, **5***, **6*** and **7***), but in four compounds (*i.e.*, **2***, **3***, **2'***, and **3'***) it is considerably large, *i.e.*, *ca.* 3.7. The larger S values may be explained in terms of the factors illustrated in Figure 2, *i.e.*, (A) the presence of two coplanar zigzag chains,[12] each of which contains the C-1 atom[13]

(9) S. Yamana, *J. Org. Chem.*, **33**, 1819 (1968).

(10) The oblique lines of Figure 1 are the standard lines.[7] In order to simplify Figure 1, the horizontal lines are omitted. The intersections of the standard lines and the horizontal lines are indicated by ⊖.

(11) Carbohydrates are numbered as follows (the mark * means that we are dealing with a glycopyranosyl compound, RX): **1***, 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl; **2***, 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl; **2'***, 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl; **3***, 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl; **3'***, 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl; **4***, 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl; **5***, 2,3,4,6-tetra-*O*-acetyl-α-D-talopyranosyl; **6***, 1,3,4,5-tetra-*O*-acetyl-β-D-fructopyranosyl; **7***, 1,3,4,5-tetra-*O*-acetyl-α-L-sorbopyranosyl.

(12) A coplanar chain is a chain composed of some atoms, all of which lie in one plane.

(13) The C-1 atom is the one to which the OH radical is attached. Moreover, these two coplanar zigzag chains contain a common moiety, *i.e.*, the O*–C-1 bond.

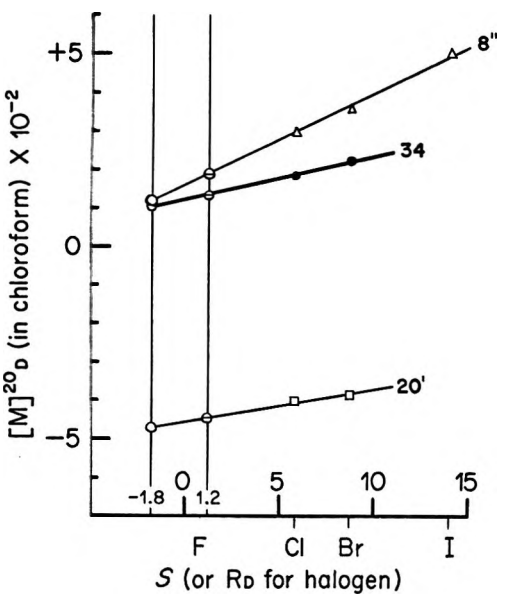

Figure 4.—Estimations of the S value of H and OH in steroid derivatives:[17,20] A 2 class (S of H = −1.8; S of OH = 1.2). O, H; ⊖, OH.

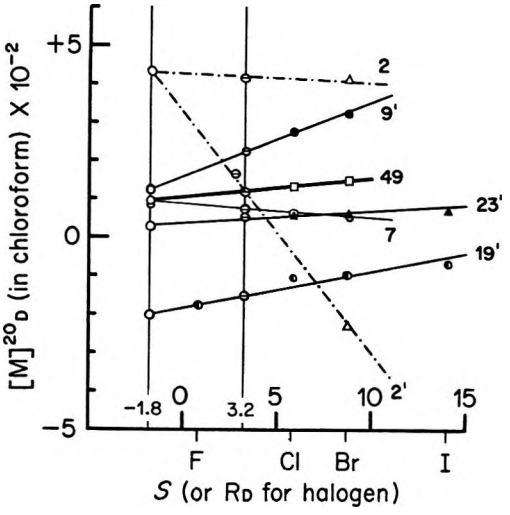

Figure 5.—Estimations of the S value of H and OH in steroid derivatives:[17,20,22] A 3 class (S of H = −1.8; S of OH = 3.2). O, H; ⊖, OH.

[the first one is C-1–O*–C-5–C-6–(OAc)-6t[14] and the second one is O*–C-1–C-2–(OAc)-2(down)]; (B) the presence of the Ac radical at the end of each of these coplanar zigzag chains.

These two conditions are easily seen when one compares the molecular structures of the compounds which have a large S value of OH radical (*i.e.*, **2***, **3***, **2'***, and **3'***) with those of the others (*i.e.*, **1***, **4***, **5***, **6***, and **7***). Moreover, the phenomenon that the S value of the OH radical in **2'*** and **3'*** is slightly larger than that in **2*** and **3*** suggests that the extension of the first coplanar zigzag chain by a new coplanar bond C-1–(OH)-1(up) increases the S value of the OH radical.[15] In other

(14) O* means the ring oxygen atom and t means the trans position (see Figure 6 of the previous paper[9]).

(15) The increase produced by a coplanar zigzag chain (or a combination of two kinds of coplanar chains) in the S value of an OH radical which is combined (but not coplanar) with this chain (or these chains) is named the "First Coplanar Effect." The increase which is caused by extending a coplanar zigzag chain with the OH radical itself is called the "Second Coplanar Effect."

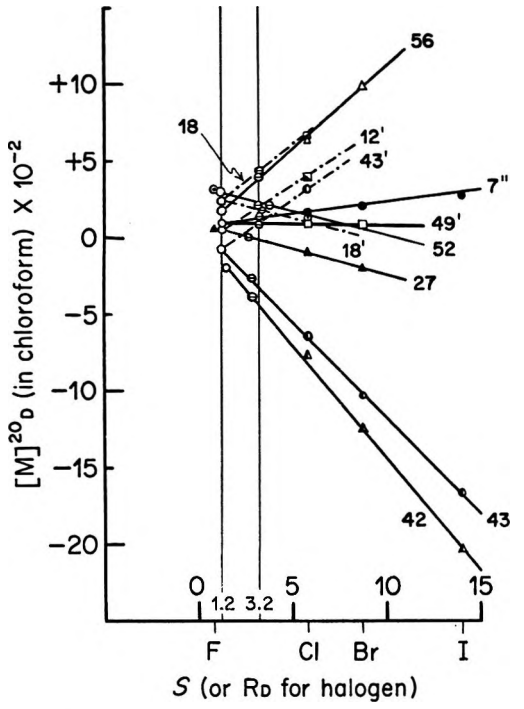

Figure 6.—Estimations of the S value of H and OH in steroid derivatives:[17,20,22] B 2′ class (S of H = 1.2; S of OH = 3.2). O, H; ⊖, OH.

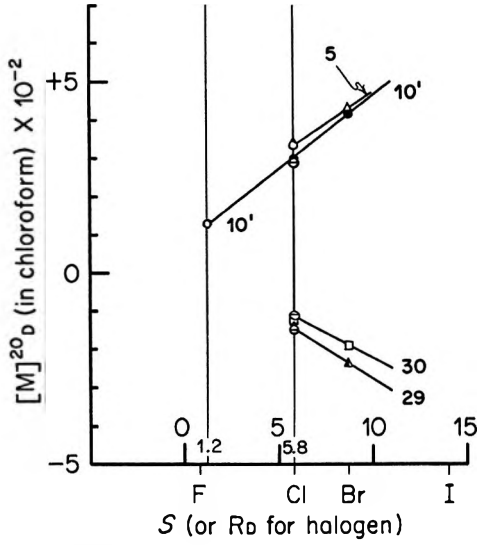

Figure 7.—Estimations of the S value of H and OH in steroid derivatives:[17] B 3 class (S of H = 1.2; S of OH = 5.8) and the case S of H = 5.8. O, H; ⊖, OH.

words, the S value of the OH radical at the 1 position in **2*** and **3*** is much larger than *ca.* 1.2 owing to the first coplanar effect, but the one in **2′*** and **3′*** is additionally increased by the second effect.

Strictly speaking, however, the actual structure of pentopyranosyl compounds is that of an equilibrium between two different conformations related by inversion of the tetrahydropyranyl ring.[16] Therefore, it becomes necessary to examine the applicability of eq 1 and at the same time the variability of the S value of OH in other types of compounds. In this article, the method is applied to steroids because of the rigid carbon skeleton of these substances. The 75 steroid derivatives, RX, discussed in this article and their molecular rotations are given in Table I.

(16) P. L. Durette and D. Horton, *Carbohyd. Res.*, **18**, 57 (1971).

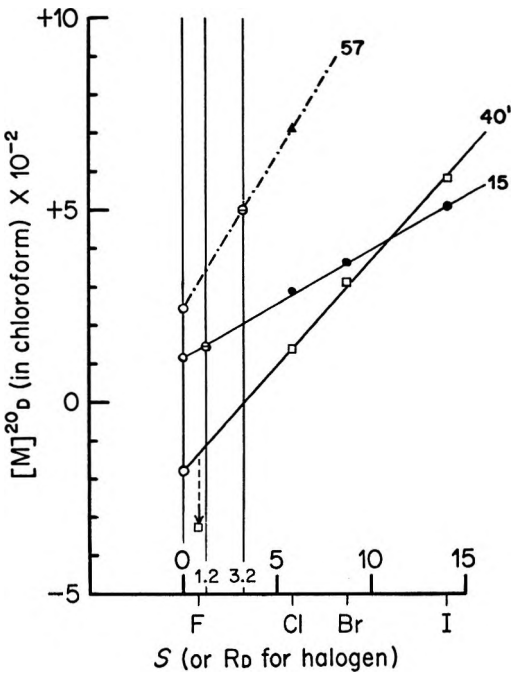

Figure 8.—Estimations of the S value of H and OH in steroid derivatives:[17,21,22,25] C 1′ class (S of H = 0.0; S of OH = 1.2); C 2 class (S of H = 0.0; S of OH = 3.2). O, H; ⊖, OH.

The $[M]^{20}D$ values[17] were plotted against the S (or R_D) value of the halogen atom to get the standard lines of Figures 3–8, but the values of S used are as follows: S of F atom is 0.8; S of Cl atom is 5.8; S of Br atom is 8.7; S of I atom is 14.0.[18] Next, the S values of the H atom and that of the OH radical were estimated. However, in the present instance, not only the S value of the OH radical but also that of the H atom were obtained by using only the ITL method,[8,19] because, as will be noticed later, the S value of the H atom depends on the orientation of the corresponding C–H bond and therefore the method using the intersection of two standard lines of a pair of diastereomers (as shown in Figures 1 and 3 of the previous paper[4] for the case of carbohydrates) is unsuitable.

The intersections formed by the ITL method are shown by the white circles (for the H atom) and the marks ⊖ (for the OH radical) in Figures 3–8.[20–22]

It is apparent from Figures 3–8 that H and OH can

(17) Refer to Table I.

(18) A. I. Vogel, *J. Chem. Soc.*, 1833 (1948).

(19) Some of the compounds listed in Table I are unsuitable for estimating the S value of the H atom and that of the OH radical, for the following reasons. (a) A standard line may be nearly horizontal, and, accordingly, the abscissal value of the intersection of this standard line with the horizontal line (eq 2) cannot be estimated clearly on a figure (for example, **45′**, **46′**, **48′**, and **50′**). (b) A $[M]^{20}D$ *vs.* R_D (for halogen) plot is nearly horizontal and is situated too far from the horizontal line of eq 2, and, therefore, it is impossible to get their intersection at a moderate abscissal value (for example, **19**, **35**, and **41**).

(20) A $[M]^{20}D$ *vs.* R_D (for halogen) plot of a steroid which has only one substituent (*i.e.*, X) is drawn with a somewhat bold line.

(21) The symbol → means a deviation from the corresponding solid line.

(22) **2** and **2′** have a $[M]^{20}D$ datum of only one kind of halide, and therefore these two compounds do not have any standard lines. If S values for H and for OH are assumed to be −1.8 and 3.2, respectively, $[M]^{20}D$ *vs.* S (or R_D for halogen) plots for these three X's (*i.e.*, H, (OH), and one halogen atom) become straight. Accordingly, **2** and **2′** seem to belong to the A 3 class and they are shown by dotted lines in Figure 5. Similarly, four compounds, **12′**, **18**, **18′**, and **43′**, seem to belong to the B 2′ class and are indicated by the dotted lines in Figure 6. **57**, which is presumed to belong to the C 2 class, is similarly shown in Figure 8.

TABLE II
PAIR OF S VALUE OF H ATOM AND S VALUE OF (OH) RADICAL IN STEROID DERIVATIVES

Figure	Class	S value H	S value (OH)	Type[a]	Ccmpd
3	A 1	−1.8	−1.8	h	24, 25
4	A 2	−1.8	1.2	i	8″, 20′, 34
5	A 3	−1.8	3.2	c	7, 9′, 19′, 23′, 49 (2, 2′)
3	B 1	1.2	1.2	h	11, 11′, 14, 31
6	B 2′	1.2	3.2	i′	27, 42, 43, 7″, 49′, 52, 56 (12′, 18, 18′, 43′)
7	B 3	1.2	5.8	c	10′
8	C 1′	0.0	1.2		15
8	C 2	0.0	3.2	i	(57)

[a] See Figure 9.

take several discrete S values and that pairing of the S values of H and OH will lead to a certain classification. Depending on the S value of the H atom (*i.e.*, −1.8, 1.2,[23] or 0.0), the pairs are divided into three main classes (*i.e.*, A, B, and C classes, respectively), each of which is again divided into several subclasses, as shown in Table II.[24]

In order to distinguish visually the various kinds of S value pairs from each other, Figure 9 has been constructed, in which the ordinate corresponds to the S value and the abscissa corresponds to the kind of atom or radical.

It is clear from Figure 9 that there are several kinds of slopes. The main types are named as follows: (a) *horizontal* (or h) type—A 1 class and B 1 class; (b) *gently increasing* (or i′) type—B 2′ class; (c) *increasing* (or i) type—A 2 class; (d) *climbing* (or c) type—A 3 class and B 3 class.

Next, the series of compounds RX, where either the $[M]^{20}D$ value of the hydride (*i.e.*, X = H) or that of the hydroxide (*i.e.*, X = OH) is known, were treated in similar fashion. The results are given in Figures 7, 8, and 10–13 (S of H = −1.8 in Figure 10, S of H = 0.0 in Figure 8, S of H = 1.2 in Figure 11, S of H = 5.8 in Figure 7, S of (OH) = −1.8 or 1.2 in Figure 12, and S of (OH) = 2.2 or 3.2 in Figure 13).[25]

The S values of H and those of OH obtained from Figures 7, 8, and 10–13 are listed in Table III.[26]

From Figures 3–8 and 10–13 and Tables II and III, the following empirical rules are obtained for the steroids.

Rule 1.—$[M]^{20}D$ *of a compound RX (where X is H, OH, F, Cl, Br, or I)* $= a + bS$, *but here a and b are constants which are inherent in the moiety R, and S is one which is concerned with some optical property of X.*

(23) The S value of H, 1.2, is approximately, but not exactly, equal to the R_D value of the H atom in CH_2 (1.028).[18]

(24) The A 2 class was already encountered in the carbohydrates.[4,6,9]

(25) In the case of **51** (Figure 10), the standard line was drawn by using the $[M]^{20}D$ value of the bromide and the iodide. This line was useful to get the S value of H atom, −1.8. The $[M]^{20}D$ value of the chloride does not fall, however, on this standard line at the abscissal value of 5.8 (R_D of Cl atom[18]). Moreover, in three cases (*i.e.*, **35′** (in Figure 13), **36′** (in Figure 11) and **40′** (in Figure 8)), the $[M]^{20}D$ values of their fluorides do not fall on their respective standard lines (all of which are drawn without using the $[M]^{20}D$ values of fluorides) at the abscissal value of 0.8 (R_D of F atom[18]). The study of the reasons for these abnormalities of fluorides is left for the future.

(26) The S value of the H atom is, in some cases, somewhat large (either positive or negative in sign). For example, S of H = *ca.* −7 in **35′**, **37′**, and **40** or *ca.* 14 in **3**, **15″**, and **32**. These S values are somewhat imprecise and are not included in any figures or tables of this article. (Refer to footnote 31.)

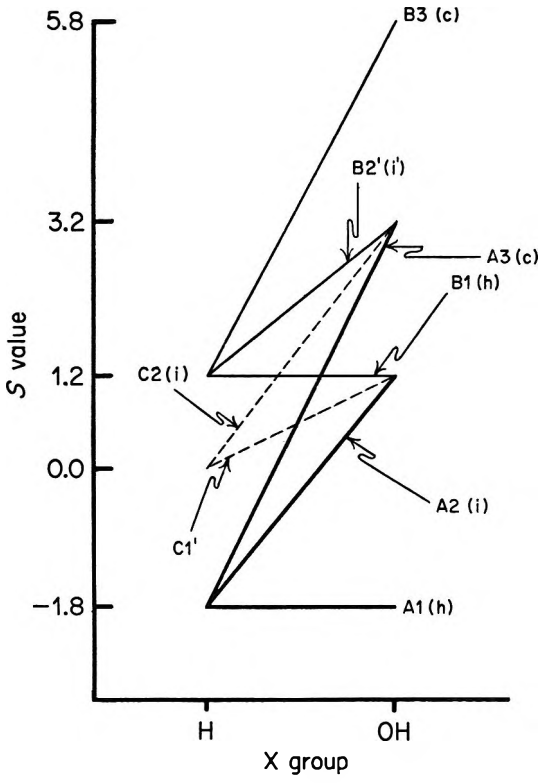

Figure 9.—Types of line slopes which corresponds to a pair of S values (*i.e.*, S value of H atom and S value of OH radical: h, *horizontal;* i, *increasing;* i′, *gently increasing;* c, *climbing*).

TABLE III
S VALUE OF H ATOM OR S VALUE OF (OH) RADICAL IN STEROID DERIVATIVES

Figure	S of H	Compd
10	−1.8	1, 4″, 6′, 13, 39′, 51, 53
8	0.0	40′
11	1.2	3′, 4, 6, 8, 34′, 36′, 44, 47′, 54, 55
7	5.8	5
Figure	**S of (OH)**	**Compd**
12	−1.8	16
12	1.2	16″, 17″, 21′, 22, 26
13	2.2	17, 35′, 37′
13	3.2	22′, 28, 33, 38′
7	5.8	29, 30

Rule 2.—*The value of S is equal to the value of atomic refraction,* R_D *only for halogen.*

Rule 3.—*A hydrogen atom (or a hydroxyl radical) assumes discontinuous definite S values, which are as follows:*[27] *H atom (−1.8, 0.0, 1.2, etc.);*[26] *OH radical (−1.8, 1.2, 2.2, 3.2, 5.8, etc.).*

Rule 4.—*In the same series of compounds, S value of H atom* ≤ *S value of OH radical.*

Moreover, in terms of molecular structures, the following rules can be deduced.

Rule 5.—*The S value of the H atom or OH radical depends on the orientation of the corresponding C–H (or C–O) bond.*

For example, the S value of the H atom is −1.8 in some compounds (*i.e.*, **6′**, **34**, and **49**), but it is 1.2 in their diastereomers (*i.e.*, **6**, **34′**, and **49′**). Similarly, the S value of the OH radical is 1.2 in **22**, but it is 3.2 in **22′**.

(27) Only those S values which are ascertained in more than three cases in this article are given here.

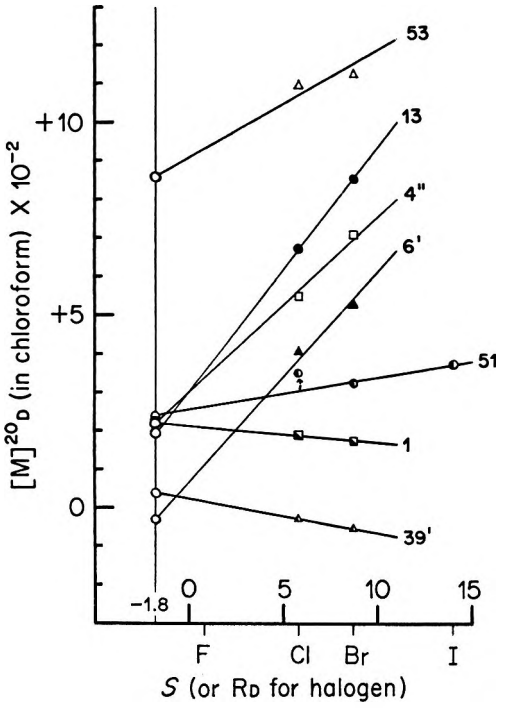

Figure 10.—Estimation of the S value of H in steroid derivatives[17,21,25] (S of H = −1.8); O, H.

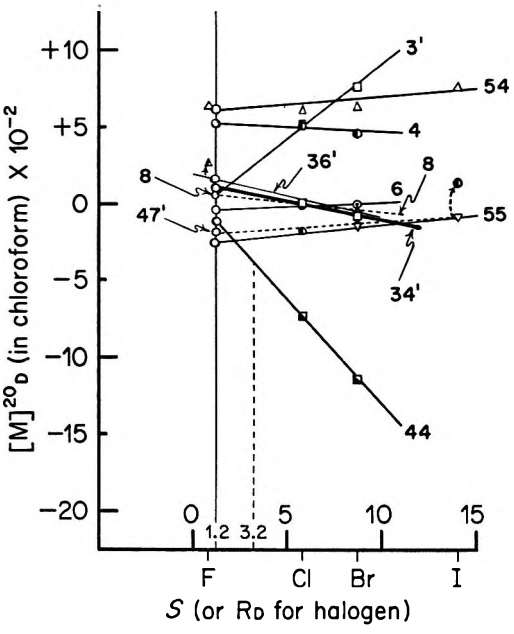

Figure 11.—Estimation of the S value of H in steroid derivatives[17,20,21,25] (S of H = 1.2); O, H.

Rule 6.—*When the X group is located more or less in the plane of symmetry with regard to the arrangement of the atoms which surround it, the compound belongs to the horizontal type class.*

For example, **24** and **25** (A 1 class); **11**, **11'**, **14**, **31** (B 1 class).

Rule 7.—*When there is a double bond at the α position (with respect to the X group) and in the same ring of the steroid skeleton, the compound belongs to the B 2' class (i.e., S of H = 1.2; S of (OH) = 3.2).*

The examples are **12'**, **18**, **18'**, **42**, **43**, **43'**, and **56**. The only exception is **57**, which belongs to the C 2 class (S of H = 0.0; S of (OH) = 3.2). Referring to Table III, the S value of the H atom is 1.2 in **44**, but, as $[M]^{20}D$ of the corresponding hydroxide is unknown in Table I, the S value of the OH radical cannot be estimated in **44**. However, **44** (*i.e.*, 7α-X-3β-chlorocholest-5-ene) has a double bond between C-5 and C-6 which is located at the α position with respect to the X-7 group; hence, according to rule 7, it is presumed that **44** belongs to the B 2' class and the S value of OH radical which is attached to the 7 position in α orientation may be 3.2. This value is used in Figure 11 to estimate the $[M]^{20}D$ value of the hydroxide of **44** (in which X is OH radical) at *ca.* −400.

Rule 8.—*If the X group and some other group Y lie on the same coplanar zigzag chain,[12] the influence of the Y group can be easily transmitted to the X group.*

In order to illustrate rule 8, Table IV is given here.[28]

TABLE IV

INFLUENCE OF Y-6 GROUP ON THE S VALUE OF THE OH RADICAL AT THE 3 POSITION

		—S of X-3α—				—S of X-3β—	
Compd	Y-6	H	(OH)	Compd	Y-6	H	(OH)
11	Two H's	1.2	1.2	11'	Two H's	1.2	1.2
22[b]	O (in CO)	*a*	1.2	22'[c]	O (in CO)	*a*	3.2

[a] Unknown. [b] This has a noncoplanar structure, (CO)-6-C-5-C-4-C-3-(OH)-3α. [c] This has a coplanar zigzag chain, (CO)-6-C-5-C-4-C-3-(OH)-3β.

Table IV shows that the replacement of two hydrogen atoms by an O atom to make a carbonyl group at the 6 position changes the S value of the OH at C-3 from 1.2 to 3.2 only when this OH radical is in the β orientation which is coplanar with the carbonyl radical.[29]

Another example illustrating rule 8 is given in Table V.[28]

TABLE V

INFLUENCE OF Y-3α GROUP ON THE KIND OF CLASS

			—S of X-2β—	
Compd[a]	Y-3α	Class	H	(OH)
9'	Cl	A 3 (c)	−1.8	3.2
10'	Br	B 3 (c)	1.2	5.8

[a] This has a coplanar zigzag chain, Y-3α-C-3-C-2-X-2β.

As shown in Table V, the kind of group at the 3α position determines the class to which **9'** or **10'** belong, although, interestingly enough, both classes are of the same, *i.e.*, *climbing*, type. In other words, the change from Cl to Br (both of which are halogen) does not cause any change in class type but produces a parallel displacement of the line of the class type in Figure 9. In order to examine whether this phenomenon also exists in the corresponding noncoplanar structures (Y-3β-C-3-C-2-X-2α),[29] the $[M]^{20}D$ values of some other compounds (*i.e.*, 2α-X-3β-chloro-(5α)cholestane and 2α-X-3β-bromo-(5α)cholestane) are necessary. Unfortunately, these are not available, but, in order to show the correctness of rule 8, some other examples will be given later in this article.

Interpretation from the Standpoint of Electronic Theory.—As regards the electron density on a hydrogen atom which is combined with a carbon atom in a steroid skeleton, the following situation may be probable. A hydrogen atom has a smaller electronegativity than a carbon atom, and therefore a partially ionized bond

(28) Refer to Tables II and III.
(29) See Figure 14.

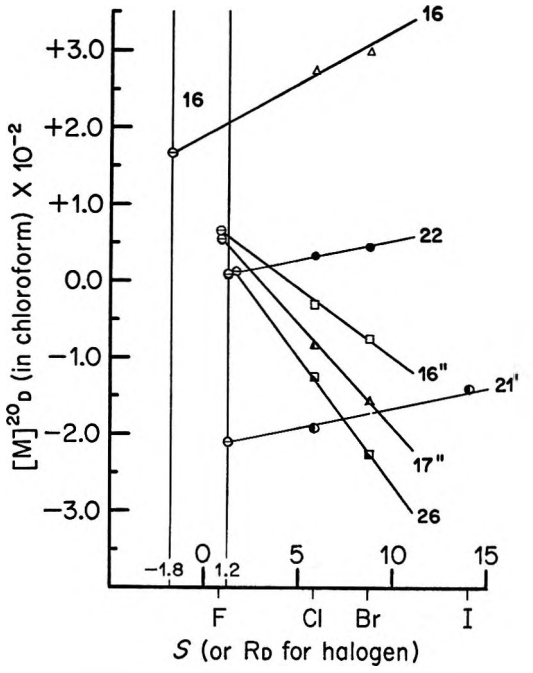

Figure 12.—Estimation of the S value of OH in steroid derivatives[17] (S of OH = −1.8 or 1.2); ⊖, OH.

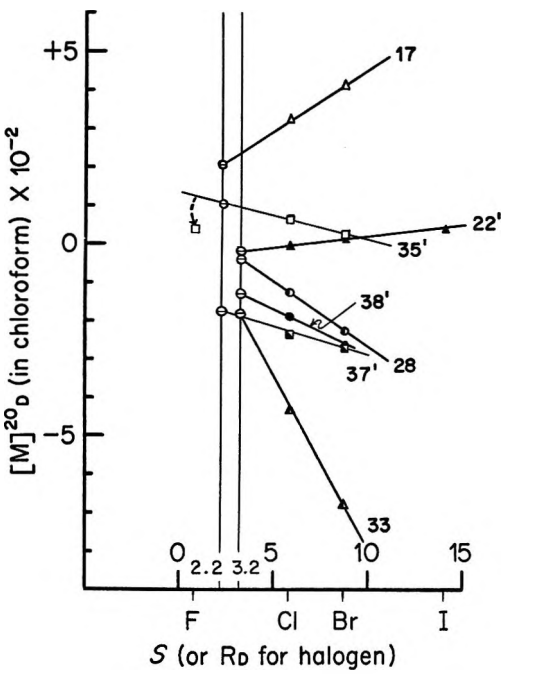

Figure 13.—Estimation of the S value of OH in steroid derivatives[17,21,25] (S of OH = 2.2 or 3.2); ⊖, OH.

$C^{\delta-}$–$H^{\delta+}$ is more stable than a perfectly electroneutral covalent bond C–H. However, if an atom or radical Y in the remainder of the molecule repulses an electron toward this $C^{\delta-}$–$H^{\delta+}$ bond, from the opposite side of $H^{\delta+}$, $H^{\delta+}$ will be forced to receive a part of an electron and to become electroneutral H. Then, depending on the magnitude of the electron-repulsing (or -attracting) force of the Y group, roughly speaking a carbon–hydrogen bond may exist in the two states, C–H or $C^{\delta-}$–$H^{\delta+}$.

On the other hand, it has been reported that the R_D value of an H atom (in CH_2) is positive in sign, 1.028,[18] but a proton H^+ has a negative refractivity.[30] On this basis, the several discrete S values of H atom given in rule 3 can be interpreted as follows: the S value of H in C–H is 1.2 and the S value of H in $C^{\delta-}$–$H^{\delta+}$ is −1.8. The case where the S value of H is equal to 0.0 may be a mixture of the two states of a carbon–hydrogen bond.[31] One way of showing the correctness of this interpretation is to compare **3'** with **4''**.[28] The S value of the H-2β atom is 1.2 in **3'** which does not have any halogen atom attached to the C-2 atom of the steroid skeleton, but it is −1.8 in **4''** in which the Cl-2α atom is supposed to attract an electron from the H-2β atom through the coplanar chain, Cl-2α–C-2–H-2β.

In order to examine the correctness of rule 8 and the author's interpretation of the reasons for the variability in the S value of H, some examples are shown in Table VI.[28]

Table VI shows that the Y-3α group in the second column attracts an electron more strongly than that in the fifth column of the same line. This influence of the Y-3α group is transmitted to the H-2β group through the coplanar zigzag chain, Y-3α–C-3–C-2–H-2β.[29]

The other coplanar zigzag chain, Y-2β–C-2–C-3–X-3α, and its corresponding noncoplanar structure, Y-2α–C-2–C-3–X-3β, are treated in Tables VII and VIII, respectively.[28,29]

TABLE VI

INFLUENCE OF Y-3α GROUP ON THE S VALUE OF H-2β AND THE KIND OF CLASS-TYPE

Compd[a]	Y-3α	S of H-2β	Compd[a]	Y-3α	S of H-2β	Type[b]
25[c]	O (in CO)	−1.8	11	H	1.2	h
8''	OAc	−1.8	7''	OH	1.2	i or i'
9'[d]	Cl	−1.8	10'	Br	1.2	c

[a] This has a coplanar zigzag chain, Y-3α–C-3–C-2–H-2β. [b] See Figure 9. [c] Strictly speaking, the O–C-3 bond is not coplanar with the C-2–H-2β bond. [d] 9' and 10' have already been included in Table V, with the S values of their OH radicals.

TABLE VII

INFLUENCE OF Y-2β GROUP ON THE S VALUE OF X-3α GROUP

		S of X-3α	
Compd[b]	Y-2β	H	(OH)
11	H	1.2	1.2
14	OH	1.2	1.2
15	OAc	0.0	1.2
13	CO[c]	−1.8	*a*
16	Cl	*a*	−1.8
17	Br	*a*	2.2

[a] Unknown. [b] This has a coplanar zigzag chain, Y-2β–C-2–C-3–X-3α. [c] Strictly speaking, the O–C-2 bond is not coplanar with the C-3–X-3α bond.

TABLE VIII

INFLUENCE OF Y-2α GROUP ON THE S VALUE OF X-3β GROUP

		S of X-3β	
Compd[b]	Y-2α	H	(OH)
11'	H	1.2	1.2
16''	Cl	*a*	1.2
17''	Br	*a*	1.2

[a] Unknown. [b] This has a noncoplanar structure, Y-2α–C-2–C-3–X-3β.

(30) R. J. W. Le Fèvre in "Advances in Physical Organic Chemistry," Vol. 3, V. Gold, Ed., Academic Press, London, 1965, p 1.

(31) In some instances, the S value of the H atom is somewhat larger in magnitude,[26] but, when one examines the molecular structures giving rise to these values, one finds that in some of those compounds the H atom is situated at the α position with regard to a CO radical (*i.e.*, in **3**, **32**, and **40**) or to some other functional group which is conjugated with a CO radical (*i.e.*, in **35'**). This suggests that, in these compounds, some kind of constitutional change is involved (for example, keto–enol tautomerism, etc.). The study of these cases is, however, left for the future.

Table VII, which lists compounds containing a coplanar zigzag chain, shows that the S value of the OH-3α radical is not constant but depends on the kind of Y-2β group. On the other hand, Table VIII, which lists compounds containing a noncoplanar chain, shows that the S value of the OH-3β radical is constant and independent of the kind of Y-2α group. One concludes that, although the direct distance between the Y-2 group and the OH-3 radical is much larger in the coplanar zigzag chain, *i.e.*, in the trans conformation, than in the noncoplanar structure, *i.e.*, in the gauche conformation, the influence of the Y-2 group is easily transmitted to the OH-3 radical only through a coplanar zigzag chain.

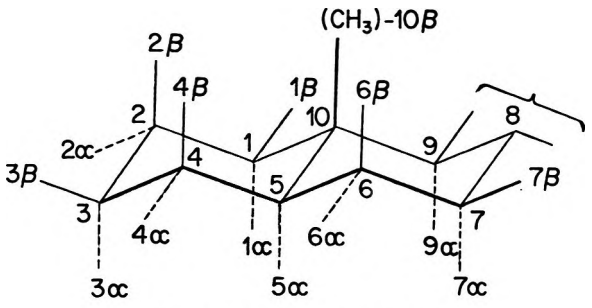

Figure 14.—Steroid skeleton.

Conclusion

Several theories (or calculation methods) have been presented for estimating the optical rotation of an organic compound.[32] Some of these emphasize the role of the atomic refraction, R_D (or polarizability, α), of an atom (or a radical) in producing the optical rotatory power of a molecule. However, none of them pay any attention to the variability of or the nature of the change in this R_D (or α) value. Moreover, since the days of van't Hoff,[33] the role apparently played by the presence or absence of a coplanar zigzag chain has never been noticed. It is hoped that the empirical rules 1–8 presented in this article will be of help in constructing a new theory or developing new approaches to the calculation of optical rotatory power.

Addendum.—The fact that a straight $[M]^{20}D$ *vs.* S line changes its slope, according to the change in the kind of a Y atom (or radical) which is coplanar with the X atom (or radical) in the same molecule, means that these two atoms (or radicals) (*i.e.*, X and Y) couple with each other to produce a certain partial molecular rotation, in spite of their existence in one plane (*cf.* 7'', 9', and 10'; 11, 14, 16, and 17; 11', 16'', and 17'', etc.).

(32) J. H. Brewster, in "Topics in Stereochemistry," Vol. 2, N. L. Allinger and E. L. Eliel, Ed., Interscience, New York, N. Y., 1967, p 1.
(33) van't Hoff, *Bull. Soc. Chim. Fr.*, **23**, 298 (1875).

Nonclassical Oxidation of Aromatics. I. Cobaltic Ion Catalyzed Oxidations of *p*-Cymene, *p*-Ethyltoluene, and *sec*-Butyltoluenes[1]

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Co(III) ion catalyzed oxidation of alkyltoluenes with oxygen was studied under mild conditions. It was found that the methyl group was preferentially oxidized in the presence of other groups on the same benzene ring. *p*-Cymene afforded *p*-isopropylbenzoic acid (90%) and *p*-methylacetophenone (10%) as the primary products. *p*-Ethyltoluene gave *p*-ethylbenzoic acid (68%) and *p*-methylacetophenone (25%) as major products. Prolonged oxidation converted *p*-methylacetophenone into *p*-acetobenzoic acid and eventually into terephthalic acid. A mixture of the isomeric *sec*-butyltoluenes was oxidized to the corresponding *sec*-butylbenzoic acids (89%). The relative ease of oxidation of the alkyl groups follows the sequence methyl > ethyl > isopropyl ~ *sec*-butyl. These results cannot be rationalized on the basis of the classical free-radical mechanism, and an electron-transfer mechanism involving the intermediacy of radical cations is proposed.

The literature has numerous references to the oxidation of various alkyltoluenes in which secondary or tertiary hydrogen on alkyl groups is preferentially abstracted. In fact, the oxidation of the methyl group in such instances is difficult. Products are comprised of carboxylic acids, hydroperoxides, and/or cleavage products of the latter. Oxidation of *p*-cymene or *p*-ethyltoluene with 15% nitric acid is reported to produce *p*-toluic acid, whereas *p*-ethylisopropylbenzene affords *p*-ethylbenzoic acid.[2] In the autoxidation of *p*-ethyltoluene[3] or *p*-cymene,[4-7] major products were either *p*-toluic acid, terephthalic acid, *p*-methylacetophenone, or a combination of these. *p*-Acetobenzoic acid, *p*-isopropylbenzoic acid, and *p*-(α-hydroxyisopropyl)-benzoic acid were also formed in varying amounts. The relative ease of oxidation of these alkyl groups follows the sequence isopropyl > ethyl > methyl. In this paper, we report on a study of Co(III) ion catalyzed oxidation of a methyl group in preference to isopropyl, ethyl, or *sec*-butyl in *p*-cymene, *p*-ethyltoluene, and *sec*-butyltoluenes. Results obtained are surprising as the normal order of hydrogen abstraction, tertiary > secondary > primary, is reversed.

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Results

Reactants, experimental conditions, and the results obtained are summarized in Table I. Conversion in all experiments was essentially 100%.

Oxidation of *p*-cymene gave *p*-isopropylbenzoic

TABLE I

OXIDATION OF ALKYLTOLUENES[a]

Expt no.	1	2[b]	3	4
Hydrocarbon oxidized	*p*-Cymene		*p*-Ethyltoluene	*sec*-Butyltoluenes[c]
Reactants, g				
$Co(OAc)_2 \cdot 4H_2O$	20	20	20	20
MEK	20	20	20	20
HOAc	400	400	400	400
n-C_4H_{10}	70	85	60	100
Substrate	53	60	20	62
Conditions				
Induction time, hr	1.0	0.5 min	0.7	0.5
Reaction time, hr	1.5	1.5	0.7	1.5
Products, g (%)				
p-Isopropylbenzoic acid	58.5 (90)	10.6 (19)		
p-Acetobenzoic acid	6.5 (10)	4.0 (7.3)	0.7 (2)	
p-Ethylbenzoic acid			16 (68)	
sec-Butylbenzoic acids				66.0 (89)[d]
p-Toluic acid		9.3 (17)	1.3 (5.5)	
p-Methylacetophenone		30 (55)	5.5 (25)	
Terephthalic acid		1.0 (1.8)	Trace	

[a] 105°, 22 atm total pressure (partial pressures of butane and oxygen). [b] 20 g of LiCl added. [c] 36.5% para, 59.0% meta, and 4.5% ortho. [d] 38.3% para, 59.5% meta, and 2.2% ortho.

acid and *p*-acetobenzoic acid in yields of 90 and 10%, respectively. To determine whether *p*-acetobenzoic acid was formed in competition with *p*-isopropylbenzoic acid, or as the result of secondary oxidation of the latter, one experiment was interrupted after 30 min. *p*-Isopropylbenzoic acid was shown in this case to be the only acid formed along with *p*-methylacetophenone. Formation of ketone is evidence for the competitive nature of the reaction. Prolonged oxidation of *p*-cymene for 5.5 hr resulted in significant amounts of terephthalic acid.

Oxidation of *p*-ethyltoluene under similar conditions gave *p*-ethylbenzoic acid and *p*-methylacetophenone in yields of 68 and 25%, respectively.

A mixture of *sec*-butyltoluenes (36.5% para, 59.0% meta, and 4.5% ortho) gave an 89% yield of the corresponding *sec*-butylbenzoic acids.

These results demonstrate unique and unexpected selectivity in methyl group attack in preference over other types of alkyl groups on the same benzene ring.

Discussion

The system discussed involves two basic reactions: (a) continuous conversion of Co(II) ions to Co(III), and (b) interaction of Co(III) with the aromatic substrates in the presence of oxygen. The first proceeds in the presence of methyl ethyl ketone (MEK)[9], or other promoters. As the ketone is rapidly consumed, *n*-butane was generally used as its precursor and a promoter of greater permanency to ensure complete conversions. Co(II) ions formed in the course of the second reaction are regenerated to Co(III) in the first. If neither ketone nor butane is added, Co(III) ions can be formed by interaction of Co(II) with peroxy radicals derived from the substrate alone.[8-12]

$$PhCH_2OO\cdot + Co(II) \longrightarrow PhCHO + Co(III) + OH^-$$

The major products of alkyltoluene oxidation in our work are unexpected on the basis of the classical free radical theory. A different mechanism, possibly involving an electron transfer step, may be operating. Such a mechanism, proposed by Dewar on kinetic grounds for the oxidation of *p*-methoxytoluene with Mn(III)[13] ions, apparently also applies to Co(III).[14] It would explain the fact that in *p*-xylene oxidation, in the presence of large amounts of cobaltic acetate and acetic acid solvent, the reaction does not stop at the *p*-toluic acid stage as in the oxidation using catalytic amount of cobalt salt. Attempts to rationalize this observation in terms of accepted free radical theory are inconclusive.[13,15] Recently, certain radical cations derived from methyl and *tert*-butyl substituted benzenes employing Co(III) salts have been observed directly by esr,[16] indicating electron transfer in the absence of oxygen. Additionally, oxidation of alkylbenzenes with potassium 12-tungstocobaltate(III) ions (K_5CoO_4-$W_{12}O_{36}$) imply involvement of outer-sphere electrons in radical cation formation.[17] Heiba, *et al.*,[14] and others[18,19] used the magnitude of ρ values in the Hammett σ-ρ relationship to distingush attack by Co(III) ions from the normal radical abstraction. Among their criteria for an electron-transfer mechanism are the following: (a) requirement of high concentration of metal ions in a higher valency state, (b) failure of the reactivities of aromatics to follow the normal order of hydrogen abstraction, (c) small effect of cupric ions, effective inhibitors through electron transfer, and (d) acceleration of rate by chloride ions, accompanied in some cases by nuclear and side chain chlorinations. Because of the similarity of the ρ values obtained in both the absence and presence of oxygen (-2.4[14] *vs.*

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-2.66[18]), electron transfer from toluene to Co(III) was probably involved.

Some of the above criteria were applied to our studies with oxygen. Table II demonstrates the effect of

TABLE II

EFFECT OF CATALYST CONCENTRATION ON *p*-CYMENE CONVERSION[a,b]

Catalyst[c] concn, *M*	Cymene conversion, %	Induction period, hr
0.18	100	1.0
0.09	18	3.5
0.04	2	11.0

[a] 1.2 *M* cymene and 1.0 *M* C_4H_{10} were used in cooxidation (105°, 22 atm, 1.5 hr). [b] Initiated with MEK. [c] Total cobalt ions, initially added as $Co(OAc)_2 \cdot 4H_2O$.

catalyst concentration on cymene conversion and induction period. With increasing cobalt concentration, a shortening of the induction time, as well as increasing cymene conversion, was obtained, with no effect on the selectivity to isopropylbenzoic acid. The distinguishing feature of this system is its requirement for a high concentration of metal ions throughout the reaction, not observed in free-radical processes where the metal catalyst is only effective in the early stages of the reaction.[20,21] Similar conditions are also employed in novel xylene oxidations,[22] believed to involve radical cation intermediates (Teijin process).[23] Table III summarizes reactivities for some aromatics which

TABLE III

RELATIVE REACTIVITIES OF AROMATICS TOWARD Co(III) ION[a]

p-Xylene	3.9[b]
p-Ethyltoluene	3.5
p-Cymene	2.4
o-Xylene	2.0
p-tert-Butyltoluene	1.9
Ethylbenzene	1.2
Toluene	1.0[c]
Cumene	0.1
p-Methylacetophenone	0.1
tert-Butylbenzene	0.0[d]

[a] 105°, 22 atm, in presence of MEK–C_4H_{10}. [b] Reactivity per molecule. [c] Assumed standard. [d] Internal standard.

were obtained by competitive oxidation. Reactivity data of Table III should be compared with literature values of Table IV. Reactivities observed in Co(III) systems differ from those observed with Cr(VI) where a hydrogen abstraction pattern was followed. In the Mn(III) system, the electron transfer pathway appears to be of importance only in highly activated molecules such as *p*-methoxytoluene. The reactivity sequence observed by us for alkylbenzenes, ethylbenzene > toluene > cumene, is in accord with the literature. Similarly, the reactivity order of *p*-cymene > *p-tert*-butyltoluene and their magnitude are also in reasonable agreement with the literature.[18] *p*-Xylene under our conditions was less reactive than previously reported.[14]

Even more interesting than this reactivity sequence

TABLE IV

REACTIVITIES OF AROMATICS TOWARD Co(III), Cr(VI), AND Mn(III) IONS AND SOME RADICALS (PER ACTIVE HYDROGEN)

Aromatic Hydrocarbon	Co(III), 65°[a]	Cr(VI), 30°[d]	Mn(III), 130°[f]	ROO·, 90°[g]	Cl·, 40°[h]
Toluene	1.0[b]	1.0	1.0	1.0	1.0
Ethylbenzene	1.3[b]	3.1		7.8	2.5
Cumene	0.3[b]			13.3	5.5
Diphenylmethane	0.8[c]	6.3	7.9	16.0	2.0
Triphenylmethane	0.7[c]	8.1	13.2		7.2
p-Methoxytoluene	71[b]		92[b,e]		

[a] Reference 14. [b] Per molecule. [c] Per active hydrogen, 40°.[19] [d] K. B. Wiberg, *Tetrahedron*, **8**, 313 (1960). [e] Our own extrapolation. [f] E. I. Heiba, R. M. Dessau, and W. J. Koehl, Jr., *J. Amer. Chem. Soc.*, **91**, 138 (1969). [g] G. A. Russell, *ibid.*, **78**, 1047 (1956). [h] G. A. Russell, *ibid.*, **85**, 2976 (1963).

is the competition between the methyl group and other alkyl substituents in the alkyltoluenes. Assuming that reactivity of the isopropyl group in cymene is represented by half the molar amount of *p*-acetobenzoic acid formed, and reactivity of the methyl group by the sum of the molar amount of *p*-isopropylbenzoic acid and half that of *p*-acetobenzoic acid produced, the methyl group reacts about 19 times faster than isopropyl. Applying this reasoning to *p*-ethyltoluene, its methyl group reacts about twice as fast as ethyl, even though ethylbenzene is slightly more reactive than toluene.

A recent paper[24] describes anodic oxidation of *p*-cymene in methanol *via* electron transfer to products corresponding to a reactivity of the isopropyl group as compared to methyl of about 2:1. The Co(III) system is therefore milder and more selective than electrochemical oxidation. Its selectivity can be altered by addition of chloride ions.[14] The accelerating effect of chloride ion and ensuing loss in selectivity associated with a more vigorous oxidation is exemplified by experiment 2. Under such conditions, reactivity of isopropyl group *vs.* methyl was 3.2:1, similar to values obtained in free radical oxidations [3.5:1[25] and 3.2:1 (ref *g*, Table IV)]. No ring or side chain chlorinated products were found. Chloride ion concentration was possibly not sufficient to capture the reactive radical cation, or the mechanism may have changed.

Based on the literature and our own work, a mechanism is proposed which involves the following steps: (a) interaction of Co(III) with the alkyltoluenes to form radical cations, (b) loss of α hydrogen to form radicals, (c) trapping of radicals by oxygen to form peroxy radicals, and (d) termination of peroxy radicals.

The first step involves reversible interaction of Co(III) ions with the substrate to form radical cations. This is based on the observation that the rate of oxidation can be accelerated or slowed down by adding Co(III) or Co(II) ions, respectively. In the next step, benzyl radicals are formed from the radical cation intermediate by loss of α hydrogen as protons. The loss of proton is controlled by stereoelectronic considerations and not by the thermodynamic stability of the product. The rate-determining step could be either K_{eq} or k_2, or both, depending on the ionization potential of the substrate and the stability of radical cation formed.

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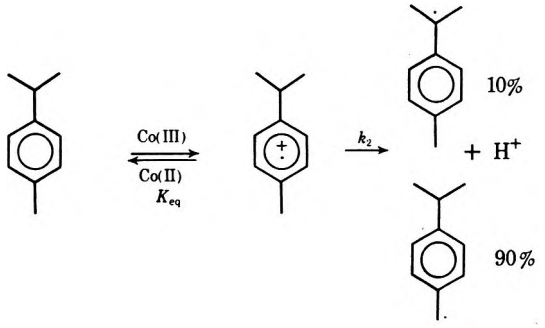
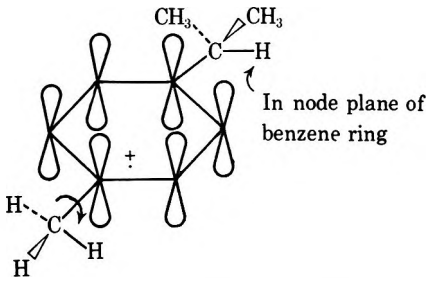


In the preferred geometry, the tertiary hydrogen on the isopropyl group of *p*-cymene is located in the node plane of the benzene ring where its interaction with the π system in the transition state is minimized. The methyl group, on the other hand, rotates freely and is therefore affected preferentially. Recent esr data support the proposed orientation of alkyl groups in radical cations on the basis of R values[26] (ratio of β-proton coupling constant to the corresponding methyl proton coupling constant: R = 0.3 for isopropyl, no rotation; 1.0 for ethyl, free rotation at 25°). Such remarkable selectivity prevails during the oxidation of *p*-cymene and *sec*-butyltoluenes, and to a lesser extent in *p*-ethyltoluene.



Precisely what is involved, induction, hyperconjugation, solvation, mass effects, or any combination of the factors, lies beyond the scope of this paper. Benzyl radicals add oxygen to afford peroxy radicals which then may terminate in several different ways which do not necessarily proceed through a hydroperoxide stage. Some of these possibilities have been recently discussed.[27] In the absence of detailed kinetic data, it is difficult to predict which of the proposed possibilities, if any, are applicable under our experimental conditions.

Experimental Section

Apparatus and Materials.—Oxidations were carried out in a 1-l., 316 stainless steel, magnetically stirred autoclave (Autoclave Engineers, Inc., Erie, Pa.) at 105° and 22 atm of total pressure. The autoclave was equipped with a cooling coil and heaters, and was connected to an oxygen supply system, temperature and pressure controllers, and recording instruments. Complete conversion of aromatics was obtained in most experiments, whereas recovery of products was usually 95% or better. The nmr spectra were obtained on a Varian T-60 spectrometer (DMSO-d_6, TMS). Chemical shifts are in δ units, in parts per million. The ir spectra were recorded either on Perkin-Elmer Infracord or Model 237B spectrometers. Carboxylic acids were analyzed by vapor phase chromatography (vpc) as trimethylsilyl derivatives (4 ft × 0.25 in. OV-1 column, programmed from 50 to 250° at 10°/min).

p-Cymene and *p*-ethyltoluene were purchased from Chemical Samples Co., Columbus, Ohio (minimum purity of 99+%), and were used as received. *sec*-Butyltoluenes, bp 193–198°, and other hydrocarbons were obtained from this laboratory.

Oxidation of *p*-Cymene.—A mixture consisting of 20 g of $Co(OAc)_2 \cdot 4H_2O$, 20 g of MEK, and 53 g (0.39 mol) of *p*-cymene in 400 g of glacial acetic acid was charged into the autoclave. After addition of 70 g of *n*-butane by means of Milroy pump, the autoclave was pressured with oxygen to 10 atm and heated to 105°. Additional oxygen was introduced to bring the pressure inside the autoclave to 22 atm. After an induction period of 1 hr, reaction was continued for 1.5 hr. The autoclave was cooled and depressured, and the product mixture was removed. The low-boiling components were removed under reduced pressure in a rotary evaporator, and 500 ml of ice water was added to the residue. The white precipitate that formed was filtered, washed with water, and dried in a vacuum oven to give 65 g of solids. Analysis of product by vpc and nmr indicated the product to be a mixture of *p*-isopropylbenzoic acid (90%) and *p*-acetobenzoic acid (10%). This result was confirmed by vpc by doping with standards. Repeated crystallization of crude material from aqueous acetic acid gave pure *p*-isopropylbenzoic acid: mp 114–116° (lit.[28] mp 116–117°); nmr δ 1.26 (d, 6, CH_3), 2.95 (m, 1, CH), 7.29 (d, 2, ring), and 7.9 (d, 2, ring). A portion of isolated *p*-acetobenzoic acid melted at 203–206° (lit.[29] mp 208°), nmr δ 2.64 (s, 3, CH_3) and 8.1 (s, 4, ring).

Oxidation of *p*-Ethyltoluene.—Oxidation of ethyltoluene was carried out in a manner described for *p*-cymene. Experimental conditions and results obtained are summarized in Table I. On work-up, 16 g (68%) of *p*-ethylbenzoic acid was isolated: mp 108–110° (lit.[30] mp 113.5°); nmr δ 1.2 (t, 3, CH_3), 2.6 (q, 2, CH_2), 7.25 (d, 2, ring), and 7.88 (d, 2, ring). In addition, the acid fraction also contained 0.7 g (2%) of *p*-acetobenzoic acid, 1.3 g (5.5%) of *p*-toluic acid, and a trace of terephthalic acid (all by vpc). The neutral fraction contained 5.5 g (25%) of *p*-methylacetophenone, whose ir spectrum and relative retention time were identical with those of an authentic sample.

Oxidation of *sec*-Butyltoluenes.—Starting with 62 g of *sec*-butyltoluenes, a total of 66 g (89%) of the corresponding carboxylic acids were obtained, neutral equivalent of 175. The ratio of ring protons to that on the alkyl group by nmr was 4:9, consistent with *sec*-butylbenzoic acids. Isomeric distribution of charge and product were determined by vpc. Results are included in Table I.

Competitive Rate Study.—Competitive oxidations on mixtures of substrates were done under conditions earlier described for *p*-cymene. Results are shown in Table III. The initial concentration of each substrate was held at low value (~0.1 *M*) to minimize possible solvent effects. After the initiation period was over, reaction was allowed to proceed for 5 min. The initial charge and the pentane extract of the final mixture were analyzed directly by vpc for the disappearance of starting hydrocarbons. Analyses were carried out (Varian 1520 chromatograph, TC detector) on two columns using *tert*-butylbenzene as internal standard: 20 ft × 1/8 in., 5% Bentone 24 and DC 200 on Chrom W at 95°, and 20 ft × 1/4 in., 20% β,β'-oxydipropionitrile on Chrom W at 100°. All reactivities were related to toluene using the following expression

$$\frac{k_a}{k_b} = \frac{\log([A]_f/[A]_i)}{\log([B]_f/[B]_i)}$$

where A and B refer to concentrations of the two substrates before and after the reaction.

Registry No.—Cobaltic ion, 22541-63-5; *p*-cymene, 99-87-6; *p*-ethyltoluene, 622-96-8; *sec*-butyltoluenes, 26571-04-0.

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Synthesis of 1-β-D-Arabinofuranosylorotate and an Investigation of the Rearrangement of 2,2′-Anhydroorotidine Derivatives

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2,2′-Anhydroorotidine ethyl ester (2) was prepared by cyclization of 2-amino-β-D-arabinofurano[1′,2′:4,5]-2-oxazoline (1) with diethyl acetylenedicarboxylate. Treatment of compound 2 with 2 *N* HCl afforded 1-β-D-arabinofuranosylorotic acid 2′,6-lactone (4) which gave, after titration with 0.5 *M* KOH, potassium 1-β-D-arabinofuranosylorotate (7). Compound 2 was readily converted to 2,2′-anhydro-1-β-D-arabinofuranosyluracil-6-carboxamide (3a) by treatment with methanol saturated with ammonia at 0°. Prolonged treatment of compound 2 with methanolic ammonia gave 2-amino-2′,6-anhydro-1-β-D-arabinofuranosyl-5,6-dihydrouracil-6-carboxamide (6). A similar rearrangement was observed when compound 7 was treated with base or allowed to stand at room temperature in solution for a few days. Treatment of compound 3a with trifluoroacetic acid, which had been saturated with dry hydrogen bromide at 0°, afforded, not the expected 3′-bromo-3′-deoxyorotidine derivative, but a 3-β-D-anhydronucleoside isomeric with 3a, which was subsequently hydrolyzed to 3-β-D-arabinofuranosyluracil-6-carboxamide (11). The combined nature of the arabinosyl 2′-OH group and the pyrimidine 6-carboxyl group in close proximity has led to a number of unusual interactions and rearrangements, for which mechanisms have been proposed.

The importance of orotic acid in the biological synthesis of nucleic acid, and pyrimidine nucleotides in particular, has been well established.[1] Orotidine was first isolated from a mutant of *Neurospora crassa* by Michelson, Drell, and Mitchell,[2] who showed that it was composed of orotic acid and ribose. Subsequently, Lieberman, *et al.*,[1g] by enzymatic studies, and Fox, *et al.*,[3] by ultraviolet absorption spectroscopy proved that the ribose moiety was affixed to the N-1 position of the pyrimidine. To date, however, the only synthetic method of preparing orotidine (~10%) is that reported by Angier and Curran.[4] This consideration prompted an investigation of new synthetic routes to various derivatives of orotic acid nucleosides.

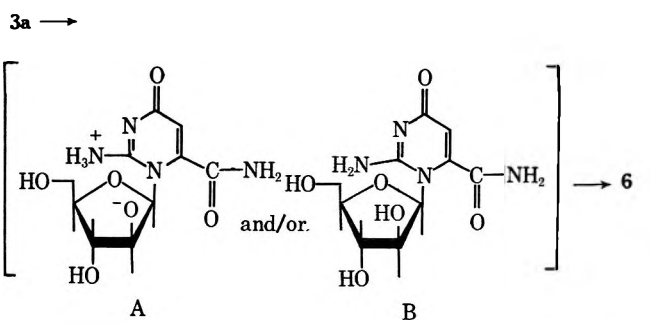
In 1968, Ferris, Sanchez, and Orgel[5] reported a synthesis of cytosine and uracil from cyanoacetylene and later, by a similar procedure, Sanchez and Orgel[6] obtained α-ribosyl- and β-arabinosylpyrimidines. Following a similar approach in our laboratory, 2,2′-anhydroorotidine ethyl ester (2) was synthesized by treatment of 2-amino-β-D-arabinofurano[1′,2′:4,5]-2-oxazoline (1) with diethyl acetylenedicarboxylate in 53% yield. This compound, like other anhydronucleosides in the literature,[7] is an important intermediate in stereochemically controlled reactions involving alteration of the sugar configuration, as well as that of the aglycon.

The potassium salt of 2,2′-anhydroorotidine (5b) was readily prepared by treatment of 2 with 1 equiv of potassium hydroxide at room temperature. Neutralization with Dowex 50 (H^+) furnished the corresponding free acid (5a).

Compound 2 was readily converted to 2,2′-anhydro-1-β-D-arabinofuranosyluracil-6-carboxamide (3a) by treatment of 2 at 0° with methanol saturated with ammonia (0°); the morpholino derivative 3b was prepared in a similar manner with the objective of obtaining a more stable protecting group for future reactions.

It was found that prolonged treatment of compound 2 at 0° with methanolic ammonia afforded 2-amino-2′,6-anhydro-1-β-D-arabinofuranosyl-5,6-dihydrouracil-6-carboxamide (6) as a side product. The structural assignment of 6 was based on the following data: uv absorption above 240 nm was lost; the nmr spectrum showed a broad singlet at δ 8.47 assigned to NH_2 and a widely separated broad doublet (22 Hz) which was attributed to the carboxamido group. This assignment was substantiated by the disappearance of the H-5 signal at δ 6.28 (singlet) and the appearance of a singlet at δ 2.8 which integrated for two protons and exchanged upon the addition of D_2O and NaOD. That the 5′ position is not involved in the anhydro linkage of 6 follows from the nmr spectrum, which showed the H-5′ protons as a broad singlet at δ 3.60.[8] In a typical 5′-anhydro derivative the H-5′ signals appear at lower field, for example at δ 4.08,[8] and as a quartet with $J_{5',5''} \sim 13$ Hz. Compound 6 was obtained in 82% yield from 2 when the same reaction was performed at room temperature in a sealed vessel for 3 days.

The formation of compound 6 can be explained by the displacement of the 2,2′-anhydro linkage of 3a through nucleophilic attack of ammonia on C-2 to form A. Attack of the initially formed 2′-O anion of A or the 2′-



(1) (a) F. W. Chathaway, *Nature*, **153**, 250 (1944); (b) H. S. Loring and J. G. Pierce, *J. Biol. Chem.*, **153**, 61 (1944); (c) H. Arvidson, N. A. Eliasson, E. Hammersten, P. Reichard, H. Von Ubisch, and S. Bergström, *ibid.*, **179**, 169 (1949); (d) L. D. Wright, C. S. Miller, N. R. Skeggs, L. L. Weed, and D. W. Wilson, *J. Amer. Chem. Soc.*, **73**, 1898 (1951); (e) R. B. Hurlbert and V. R. Potter, *J. Mol. Biol.*, **195**, 257 (1952); (f) I. Lieberman, A. Kornberg, and E. S. Simms, *J. Amer. Chem. Soc.*, **76**, 2844 (1954); (g) I. Lieberman, A. Kornberg, and E. S. Simms, *J. Biol. Chem.*, **215**, 403 (1955).

(2) A. M. Michelson, W. Drell, and H. K. Mitchell. *Proc. Nat. Acad. Sci. U. S.*, **37**, 396 (1951).

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(5) J. P. Ferris, R. A. Sanchez, and L. E. Orgel, *J. Mol. Biol.*, **33**, 693 (1968).

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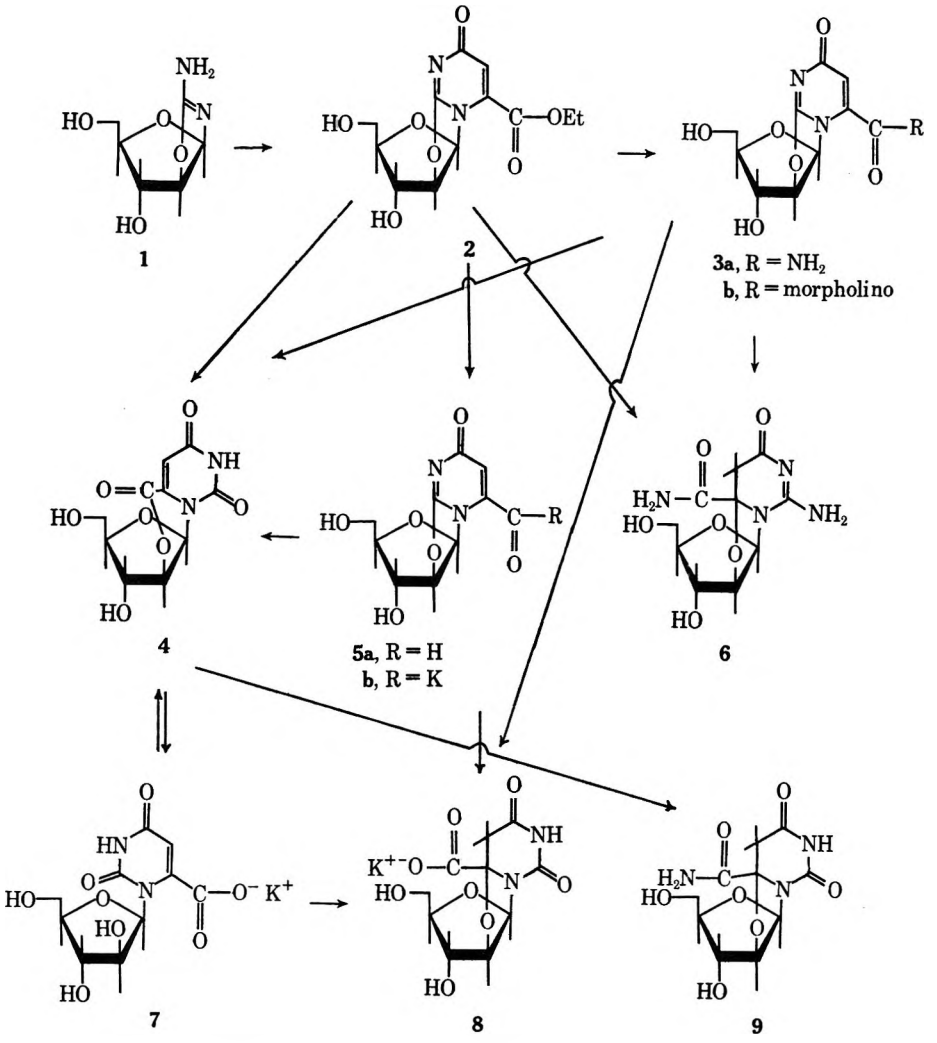
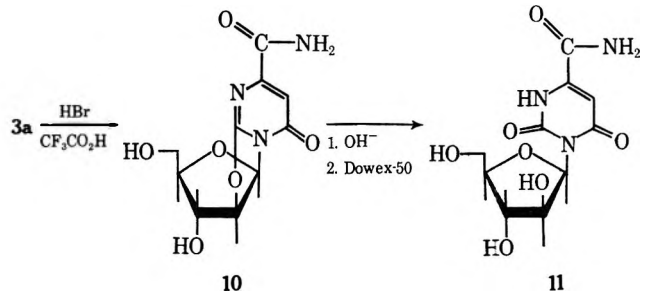
(8) B. A. Otter, E. A. Falco, and J. J. Fox, *J. Org. Chem.*, **34**, 1390 (1969).



OH group of B on C-6 would lead to the formation of the dihydro derivative **6**.

The possibility of the utilization of 2,2′-anhydroorotidine as a starting material for the synthesis of 2′-bromo-2′-deoxy nucleosides was investigated following the method described by Fox and coworkers.[9] This involves treatment of the anhydronucleoside with trifluoroacetic acid saturated with dry hydrogen bromide at 0°. This procedure, however, led to the rearrangement of compound **3a** to the corresponding 3-β-D isomer (**10**). The structure assigned to **10** is supported



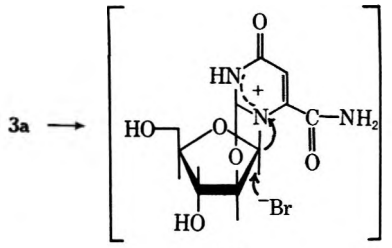
by the following data: the uv absorption spectrum showed a significant bathochromic shift of 14 nm relative to compound **3a**; and the ir spectrum of compound **10** was markedly different from that of **3a**, indicating a difference in the electronic structure of the pyrimidine moiety. In addition, the similarity of the nmr spectra of **3a** and **10** (except H-5 and H-1′) implies that both compounds have the same conformation and therefore, contain anhydro rings of the same size. Elemental analysis supports the fact that these two compounds are isomers. This structural assignment was further substantiated by the alkaline hydrolysis of compound **10** to 3-β-D-arabinofuranosyluracil-6-carboxamide (**11**). Compound **11** showed a bathochromic shift of 39 nm in alkaline solution accompanied by an increase in ϵ_{max}, characteristic of an N-3 substituted orotic acid.[3,10]

A mechanism that accounts for the above rearrangement involves protonation of **3a** to form **12**. Nucleophilic attack by bromide ion on C-1 leads to **13**, which subsequently undergoes an intramolecular displacement of the bromide ion to give compound **10**.

Further evidence for the preferential rearrangement to N-3 can be seen from orotate methylation studies.[3,4] Orotic acid may be methylated by dimethyl sulfate in alkaline medium to 3-methylorotic acid, but treatment of 3-methylorotic acid with dimethyl sulfate afforded only meager yields of 1,3-dimethylorotic acid. 1-Methylorotic acid, however, may be methylated by the same process in good yields. From an examination of a molecular model it is quite evident that the 6-carboxy function of orotic acid creates a considerable amount of steric hindrance at the N-1 position of the pyrimidine ring, and this fact would explain the difficulty in

(9) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **29**, 558 (1964).

(10) M. W. Winkley and R. K. Robins, *ibid.*, **33**, 2822 (1968).



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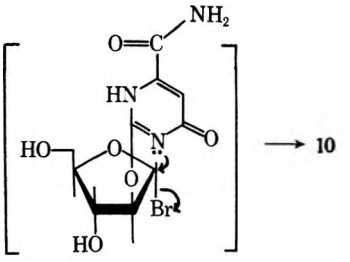


13

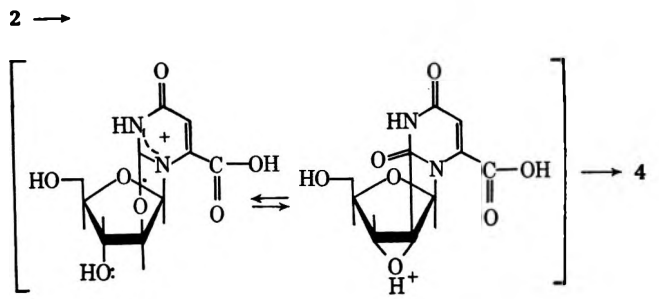
methylating orotic acid at N-1. Hence, by the same token, once glycosylic cleavage has been effected, intramolecular glycosylation will favor the formation of the more stable N-3 isomer (**10**).

Studies have shown[11] that arabinosyl nucleosides are of considerable biological interest. These conditions prompted the synthesis of 1-β-D-arabinofuranosylorotic acid from the easily accessible 2,2′-anhydroorotidine derivative. Aqueous acidic (2 *N* HCl) hydrolysis of **2** at room temperature afforded the lactone **4**.

The nmr spectrum of **4** showed an NH (δ 12.08) and H-5 as a broad singlet ($J_{5,NH}$ = 1.2 Hz) which becomes a sharp singlet after *deuteration*. It has been observed[12] that an NH, H-5 coupling in DMSO-d_6 is characteristic of many pyrimidine nucleosides, of which the orotidines are an example.

Titration of **4** with dilute potassium hydroxide readily furnished the potassium salt **7**. Potassium 1-β-D-arabinofuranosylorotate (**7**) is unstable for extended periods of time in solution at room temperature and is spontaneously converted to a corresponding dihydro derivative **8**; it is stable, however, at 0° in the dry state as the potassium salt. Attempts made to convert salt **7** to the corresponding carboxylic acid led only to reconversion to the original lactone (**4**).

It is suggested that the reaction of aqueous hydrochloric acid with the 2,2′-anhydronucleoside **2** involves as a first step hydrolysis of the ester **2** to the acid **5a** and



14 15

protonation of the pyrimidine ring to give intermediate **14**.

Intramolecular attack by the 3′-OH on C-2′ leads to the formation of a protonated "down" 2′,3′-epoxide (**15**) which can revert to **2**. Subsequent attack by the 6-carboxylic acid oxygen on C-2′ of the epoxide **15** gives lactone **4**, which upon base hydrolysis gives arabinosylorotate (**7**).

The stability of compounds **3** and **10** to acidic conditions can be explained by the fact that although the "down" epoxides can be formed, they can only be converted back to the 2,2′-anhydro starting materials, since the amide linkage is stable to acidic conditions. This acid stability of **3** and **10** rules out the possible formation of **4** by acidic hydrolysis of the anhydro linkage followed by transesterification with the C-2′ hydroxyl moiety.

In 1961 Yung and Fox[13] suggested the formation of a similar "down" protonated epoxide to account for the formation of arabinosyluracil when 2,3′-anhydroxylosyluracil was heated under reflux temperature in dilute hydrochloric acid.

A similar attempt to open lactone **4** using methanolic ammonia afforded the dihydro carboxamide (**9**). The structural assignment was based, again, on the disappearance of the H-5 vinylic proton at δ 6.42, which was accompanied by the appearance of a quartet centered at δ 2.85 (2 H, $J_{5a,5b}$ = 18.5 Hz), which exchanged upon the addition of D_2O and NaOD, and which were assigned to the 5-methylene moiety ($-CH_2$). Furthermore, loss of uv absorption at wavelengths higher than 250 nm is consistent with the dihydro structure proposed.

The combined nature of the arabinosyl 2′-OH and the pyrimidine 6-carboxyl group in close proximity have led to unusual interactions between these groups. It is interesting to point out that ring opening of the 2,2′-anhydro linkage under *acidic* conditions was accomplished only when substituents at position 6 were the ethyl ester or the free carboxylic acid group. When similar conditions were used for the hydrolysis of compound **3** and **10** (carboxamido derivatives), only the starting materials were isolated after 5 days. These observations can probably be explained by the fact that ethanol and water are better leaving groups than ammonia.

Experimental Section

General Procedure.—Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer 141 polarimeter with a 1-dm path length. Ultraviolet spectra were recorded on a Cary Model 15 spectrometer, ir spectra on a Perkin-Elmer 257 spectrophotometer (KBr pellets), and nuclear magnetic resonance spectra with a Hitachi R20a spectrometer using DMSO-d_6 as a solvent and sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard. Values given for coupling constants (Hz) and chemical shifts (δ) are first order. Microanalyses were performed by M-H-W-Laboratories, Garden City, Mich., and by Galbraith Laboratories, Inc., Knoxville, Tenn. Evaporations were carried out under reduced pressure with bath temperatures below 40°.

2,2′-Anhydroorotidine Ethyl Ester (**2**).—Diethyl acetylenedicarboxylate (12.1 g, 0.71 mol) was added to a well-stirred suspension of 2-amino-β-D-arabinofurano[1′,2′:4,5]-2-oxazoline[6] (**1**, 12.0 g, 0.69 mol) in DMAc (30 ml) and the resulting mixture was stirred overnight at room temperature. The greenish suspension

(11) (a) S. S. Cohen, *Progr. Nucl. Acid Res. Mol. Biol.*, **5**, 1 (1966); (b) F. M. Schabel, *Chemotherapy*, **13**, 321 (1968).

(12) (a) R. S. Klein, J. Wempen, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*, **35**, 2330 (1970). (b) Nmr spectra of orotidine and orotidine ethyl ester, kindly provided by Dr. B. A. Otter, showed $J_{HN,H-5}$ = 2 Hz.

(13) N. C. Yung and J. J. Fox, *J. Amer. Chem. Soc.*, **83**, 3060 (1961).

was diluted to about 40 ml with chloroform and allowed to stand for 1 hr at 4°. Filtration of the mixture afforded white crystals, mp 234–236° (11 g, 53%). A portion was recrystallized from aqueous methanol (with a trace of ethyl acetate) to furnish colorless needles: mp 235–236°; $[\alpha]^{25}D$ −194.8° (c 1.0, DMF); λ_{max}^{MeOH} 276 nm (ε 6000); $\lambda_{max}^{pH\ 1}$ 275 nm (ε 7000); $\lambda_{max}^{pH\ 11}$ 264 nm (ε 7200); nmr δ 6.85 (1, d, H-1′, $J_{1',2'}$ = 6.0 Hz), 6.48 (1, s, H-5), 5.92 (1, d, 3′-OH, $J_{3'\text{-OH}}$ = 4.2 Hz), 5.25 (1, d, H-2′), 4.97 (1, t, 5′-OH, $J_{5'\text{-OH}}$ = 4.5 Hz), 4.6–4.06 (4, m, H-3′, H-4, CH_2), 3.15–3.45 (2, m, H-5′, H-5″), 1.28 (3, t, CH_3).

Anal. Calcd for $C_{12}H_{14}N_2O_7$: C, 48.32; H, 4.73; N, 9.39. Found: C, 48.25; H, 4.90; N, 9.25.

2,2′-Anhydro-1-β-D-arabinofuranosyluracil-5-carboxamide (3a).—Methanol saturated with ammonia at 0° (200 ml) was added to compound **2** (5 g, 0.17 mol) and the suspension was stirred at 0° until complete solution was achieved. The solvent and excess ammonia were evaporated *in vacuo* and 50 ml of methanol was added to the resulting residue to afford white, crystalline **3** (4 g, 89%) mp 236° dec (softens at >221°). Recrystallization of a small portion from methanol afforded colorless crystals: mp 249° dec (softens at >225°); $[\alpha]^{22}D$ −280.0° (c 1.0, DMF); λ_{max}^{MeOH} 263 nm (ε 5900), $\lambda_{max}^{pH\ 11,1}$ 263 nm (ε 6300); nmr δ 8.39 and 8.01 (2, s, NH_2), 6.85 (1, d, H-1′, $J_{1',2'}$ = 6 Hz), 6.28 (1, s, H-5), 5.88 (1, d, 3′-OH, $J_{3'\text{-OH}}$ = 5 Hz), 5.22 (1, d, H-2′), 4.87 (1, t, 5′-OH, $J_{5'\text{-OH}}$ = 5 Hz), 4.42 (1, broad d, H-3′), 4.05 (1, broad s, H-4′), 3.25 (2, broad s, H-5′).

Anal. Calcd for $C_{10}H_{11}N_3O_6$: C, 44.61; H, 4.12; N, 15.61. Found: C, 44.64; H, 4.09; N, 15.55.

2,2′-Anhydro-1-β-D-arabinofuranosyl-6-morpholinocarbonyluracil (3b).—Compound **2** (0.5 g, 1.67 mmol) was suspended in absolute ethanol (15 ml), and morpholine (5 ml) was added. The resulting mixture was heated at reflux for 3–4 hr and then allowed to stand, at room temperature, for several days; progress of the reaction was followed by tlc on silica gel GF_{254} using 1-butanol–ethanol–water (2:1:1) as solvent system. Evaporation of the solvent and excess morpholine gave a syrup which crystallized from methanol containing a few drops of 2-propanol. Recrystallization from methanol afforded white crystals of **13** (0.5 g, 88%): mp 218–220°; $[\alpha]^{22}D$ −167.6° (c 1.0, DMF); $\lambda_{max}^{H_2O}$ 256 nm (ε 8700), $\lambda_{max}^{pH\ 1}$ 256 nm (ε 9200), $\lambda_{max}^{pH\ 11}$ 256 nm (ε 8900); nmr δ 6.36 (1, d, H-1′, $J_{1',2'}$ = 6 Hz), 6.02 (1, s, H-5), 5.99 (1, d, 3′-OH), 5.27 (1, d, H-2′), 5.0 (1, t, 5′-OH), 4.43 (1, broad d, H-3′), 4.16 (1, broad peak, H-4′), 3.8–3.2 (10, m, H-5′, morpholino protons).

Anal. Calcd for $C_{14}H_{17}N_3O_7$: C, 49.55; H, 5.05; N, 12.39. Found: C, 49.40; H, 4.92; N, 12.43.

1-β-D-Arabinofuranosylorotic Acid 2′,6-Lactone (4). Method A.—Compound **2** (1.00 g, 0.003 mol) was suspended in freshly prepared 2 *N* hydrochloric acid and the mixture was stirred at room temperature for 4 days. Evaporation of the solvent and excess acid to dryness afforded a white foam. Two successive additions and evaporations of ethanol gave a syrup which was dissolved in methanol. Crystallization occurred upon standing at 4°; filtration and subsequent washing with cold methanol afforded white crystals (0.43 g, 53%). An analytical sample was obtained by recrystallization (twice) from methanol: mp 249–250.5°; $[\alpha]^{22}D$ −25.0° (c 1.0, DMF); λ_{max}^{MeOH} 290 nm (ε 7600), $\lambda_{max}^{pH\ 1}$ 290 nm (ε 7800), $\lambda_{max}^{pH\ 11}$ 270 nm (ε 5400); nmr δ 12.08 (1, broad s, NH), 6.42 [1, broad s (becomes a sharp s after deuteration), H-5], ~5.97 [2, H-1′ (d) overlapped by 3′-OH at 5.95, $J_{1',2'}$ = 2.2 Hz], ~4.95 (2, H-2′ d at 4.97 overlapped by 5′-OH at 4.95), 4.1–4.3 (1, m, H-3′), 3.7–4.0 (1, m, H-4′), 3.47 (2, broad t, H-5′, H-5″).

Anal. Calcd for $C_{10}H_{10}O_7N_2$: C, 44.45; H, 3.73; N, 10.37. Found: C, 44.48; H, 3.92; N, 10.48.

Method B.—Compound **3a** (0.6 g, 2 mmol) was suspended in 15 ml of 0.5 *M* potassium hydroxide, and the resulting solution was stirred for 1 hr at room temperature. Treatment of the reaction mixture with Dowex 50 (H^+) (~1 g), filtration, and subsequent evaporation of the resulting filtrate afforded a foam. Water was removed by azeotropic distillation with absolute ethanol. Crystallization was effected by dissolving the crude material in ethanol and storing the solution at ~4° overnight. A small portion of this material was recrystallized from methanol to afford white crystals whose physical properties were identical with those of an authentic sample of compound **4**.

2,2′-Anhydroorotidine (5a).—Compound **2** (2.0 g, 0.006 mol) was dissolved in 25 ml of 0.5 *M* potassium hydroxide. After stirring for 5 min, the solution was treated with Dowex 50 (H^+). The solvent was evaporated and the gel was broken by azeotropic distillation with absolute ethanol. Treatment of the white residue with methanol effected crystallization (1.5 g, 81%). A pure sample was prepared by recrystallization from methanol and subsequent washing with cold methanol (with a few drops of water): mp 235–239°; $[\alpha]^{22}D$ −178.6° (c 1.0, DMF); $\lambda_{max}^{H_2O}$ 267 nm (ε 6500), $\lambda_{max}^{pH\ 1}$ 273 nm (ε 6800), $\lambda_{max}^{pH\ 11}$ 265 nm (ε 6800); nmr δ 6.89 (4, d, H-1′ at 6.89 overlapped by 3′-OH, 5′-OH, and CO_2H at ~6.8, $J_{1,2'}$ = 6 Hz), 6.40 (1, s, H-5), 5.22 (1, d, H-2′), 4.40 (1, broad s, H-3′), 4.08 (1, broad t, H-4′), 3.28 (2, d, H-5′, H-5′).

Anal. Calcd for $C_{10}H_{10}N_2O_7$: C, 44.45; H, 3.73; N, 10.37. Found: C, 44.20; H, 3.43; N, 10.18.

2,2′-Anhydroorotidine Potassium Salt (5b).—Compound **2** (1.0 g, 0.003 mol) was suspended in 0.1 *M* potassium hydroxide (30 ml, 0.003 mol) and the mixture was stirred at room temperature until the reaction was complete by tlc (about 30 min). Methanol (25 ml) was added to the warm solution and crystallization began immediately, providing 0.93 g of product (90%): mp 264° dec; $[\alpha]^{25}D$ −154.2° (c 1.0, H_2O); $\lambda_{max}^{pH\ 1}$ 273 nm (ε 6200), λ_{max}^{MeOH} 268 nm (ε 5900), $\lambda_{max}^{pH\ 11}$ 270 nm (ε 6200); nmr (D_2O) δ 7.08 (1, d, H-1′, $J_{1',2'}$ = 6.2 Hz), 6.47 (1, s, H-5), 5.45 (1, d, H-2′), 4.8–4.3 (2, m, H-3′, H-4′), 3.57 (2, d, H-5′, H-5″).

Anal. Calcd for $C_{10}H_9O_7N_2K$: C, 38.96; H, 2.94; N, 9.09. Found: C, 38.70; H, 3.00; N, 8.87.

2-Amino-2′,6-anhydro-1-β-D-arabinofuranosyl-5,6-dihydrouracil-6-carboxamide (6).—Compound **2** (1.0 g, 0.003 mol) was suspended in 100 ml of methanol saturated with ammonia (0°) in a pressurized bottle and the solution was allowed to stand for 3 days (RT). Evaporation of the solvent and excess ammonia gave a syrup. This residue was crystallized from methanol, with a few drops of 2-propanol, to furnish colorless crystals (0.75 g, 82%). An analytical sample was obtained by recrystallization of a small portion of the material from water: mp 192–194°; $[\alpha]^{22}D$ − 68.0° (c 1.0, DMF); λ_{max}^{MeOH} 234 nm (ε 12,600), $\lambda_{max}^{pH\ 11}$ 232 nm (ε 12,900), $\lambda_{max}^{pH\ 1}$ end absorption; nmr δ 8.47 (2, broad s, NH_2), 7.17 and 6.8 (2, broad s, $CONH_2$), 5.77 (1, d, H-1′, $J_{1',2'}$ = 4.5 Hz), 5.6 (1, d, 3′-OH, $J_{3'\text{-OH}}$ = 5 Hz), 4.9–5.2 (1, m, 5′-OH), 4.30–4.6 (1, m, H-2′), 3.8–4.2 (1, m, H-3′), 3.60 (3, broad s, H-4′, H-5′, H-5″), 3.39 (2, s, H_2O), 2.80 (2, s, H-5).

Anal. Calcd for $C_{10}H_{14}O_8N_4 \cdot H_2O$: C, 39.47; H, 5.30; N, 18.42. Found: C, 39.44; H, 5.50; N, 18.52.

Potassium 1-β-D-Arabinofuranosylorotate (7).—Compound **4** (0.15 g, 0.5 mmol), suspended in 17 ml of water, was titrated with potassium hydroxide (2 ml of 0.5 *M* solution). The solution was evaporated to dryness and the white residue was crystallized by adding a small amount (~15 ml) of methanol. Filtration and washing (twice with cold methanol with a few drops of water) afforded, after freeze-drying, white crystals of **7** (0.12 g, 74%): $[\alpha]^{22}D$ +26.9° (c 1.0, H_2O); $\lambda_{max}^{\sim pH\ 4.5}$ 268 nm (ε 8100), $\lambda_{max}^{pH\ 1}$ 285 nm (ε 6400), $\lambda_{max}^{pH\ 11}$ 269 nm (ε 4700); nmr δ 11.25 (1, broad s, N_3H), 5.98 (1, d, H-1′, $J_{1',2'}$ = 6 Hz), 5.35 (2, H-5, broad singlet at 5.35 overlapped by an OH), ~4 (2, H-2′, H-3′), 3.62 (3, H-4′, overlapped by the H-5′).

Anal. Calcd for $C_{10}H_{11}O_8N_2K \cdot 1/2H_2O$: C, 35.81; H, 3.58; N, 8.35. Found: C, 35.86; H, 3.50; N, 8.39.

Titration of **4** (0.15 g) with potassium hydroxide (2 ml of 0.5 *M* solution) followed by treatment with Dowex 50 (H^+) gave 0.082 g of white crystals. Recrystallization of this material from methanol afforded a pure sample, the physical properties of which were identical with those of the starting material **4**.

Potassium 2′,6-Anhydro-1-β-D-arabinofuranosyl-5,6-dihydroorotate (8). Method A.—A small portion of **7** was recrystallized from methanol containing a small amount of water to give colorless **8** which did not show any uv absorption above 240 nm: mp 218° (sinters), 222° dec; $[\alpha]^{22}D$ +29.6° (c 1.0, H_2O); nmr (with two drops of trifluoroacetic acid to effect solution) δ 10.72 (1, broad s, N^3H), 8.75 (all of the OH's overlapped by trifluoroacetic acid peak), 5.97 (1, d, H-1′, $J_{1',2'}$ = 4.7 Hz), 4.73 (1, d of d, H-2′), 4.15 (1, m, H-3′), 3.5 (3, H-5′ singlet at 3.55 overlapped by H-4′ at 3.68), 2.88 (2, q, H-5, $J_{5a,5b}$ = 17 Hz).

Anal. Calcd for $C_{10}H_{11}O_8N_2K$: C, 36.81; H, 3.30; N, 8.50. Found: C, 37.10; H, 3.50; N, 8.69.

Method B.—Crystalline **7**, when allowed to stand at room temperature, gradually lost uv absorption above 240 nm (complete loss of absorption was observed after 5 days). Nmr, ir, and uv spectra of this material are superimposable upon those of the product by method A.

Method C.—Compound **3a** (1.3 g, 0.004 mol) was suspended in 25 ml of 0.5 *M* potassium hydroxide and the resulting solution was stirred for 6 hr. The solution was neutralized by stirring

with Dowex 50 (H^+) (~1.5 g). Filtration of the resin and subsequent evaporation of the filtrate to dryness gave a white solid which crystallized from methanol to give **8** (0.9 g, 78%), mp 219°. An analytical sample was obtained by recrystallization from methanol to give white crystals, mp 222° dec. Physical properties of this material were identical with those of an authentic sample prepared previously.

Concentration of the mother liquor to about 10 ml afforded white crystals (0.20 g). Nmr, ir, and uv spectra, as well as the melting point of this material, are identical with those of lactone **4**.

Method D.—Compound **2** (0.3 g, 1 mmol) was dissolved in 10 ml of 0.5 *M* potassium hydroxide and the resulting solution was stirred at room temperature until the absorption above 240 nm was completely gone. Dilution with water (~50 ml), treatment with Dowex 50 (H^+), and subsequent evaporation of the solvent afforded a gel. This residue upon azeotropic distillation with absolute ethanol gave a syrup which crystallized from methanol after standing at ~4°. This material was shown (by ir, uv, nmr, and melting point) to be identical with compound **8**.

2′,6-Anhydro-1-β-D-arabinofuranosyl-5,6-dihydrouracil-6-carboxamide (9).—Compound **4** (0.2 g, 0.69 mmol) was stirred with 50 ml of methanol saturated with ammonia (0°). As soon as solution was effected, the solvent and excess ammonia were immediately evaporated. Addition of a small amount of methanol (~10 ml) furnished colorless crystals (0.19 g, 95%). Recrystallization from methanol (with a few drops of water) afforded pure **9**: mp 172–174° dec; $[\alpha]^{22}D$ +47.9° (*c* 1.0, DMF); nmr δ 10.35 (1, broad s, N^3H), 7.52 (2, broad s, CNH_2), 5.88 (1, d, H-1′, $J_{1',2'}$ = 4.4 Hz), 5.60 (1, broad peak, 3′-OH), 5.06 (1, broad s, 5′-OH), 4.65 (1, d, H-2′), 4.20 (1, broad peak, H-3′), ~3.64 (3, H-4′ at ~3.65 overlapped by the 2 H-5′ at ~3.64), 2.85 (2, q, H-5, $J_{5a,5b}$ = 18.5 Hz).

Anal. Calcd for $C_{10}H_{13}O_7N_3$: C, 41.81; H, 4.56; N, 14.63. Found: C, 41.67; H, 4.54; N, 14.54.

2,2′-Anhydro-3-β-D-arabinofuranosyluracil-6-carboxamide (10).—Compound **3a** (0.6 g, 0.002 mol) was suspended in 35 ml of trifluoroacetic acid saturated with hydrobromic acid (0°) and the resulting mixture was allowed to react at room temperature in a pressurized bottle overnight. Evaporation of the solvent and excess hydrobromic acid gave a foam which gradually crystallized from ethanol upon standing at ~4°. Filtration of the dark suspension afforded light gray crystals (400 mg, 67%); a second crop (~50 mg) was obtained from the mother liquor. Recrystallization from methanol with decolorization afforded white crystals (300 mg, 50%): mp 170° (sinters), 210° dec; $[\alpha]^{22}D$ −168.0° (*c* 0.4, DMF); $\lambda_{max}^{MeOH,\ pH\ 1\ and\ 11}$ 296 nm (ε 5000); nmr δ 7.85 (2, broad d, $CONH_2$), 6.58 (1, s, H-5), 6.45 (1, d, H-1′, $J_{1',2'}$ = 6 Hz), 5.91 (1, d, 3′-OH, $J_{3'\text{-OH}}$ = 5 Hz), 5.26 (1, d, H-2′), 4.95 (1, t, 5′-OH, $J_{5'\text{-OH}}$ = 5 Hz), ~4.45 (1, broad s, H-3′), ~4.14 (1, broad s, H-4′), 3.35 (2, broad t, H-5′, H-5″).

Anal. Calcd for $C_{10}H_{11}N_3O_6$: C, 44.61; H, 4.12; N, 15.61. Found: C, 44.45; H, 4.21; N, 15.35.

3-β-D-Arabinofuranosyluracil-6-carboxamide (11).—Compound **10** (0.5 g, 0.002 mol) was dissolved in 10 ml of 0.5 *M* potassium hydroxide and progress of the reaction at ambient temperature was followed by tlc on silica gel GF-254 using the solvent system ethyl acetate–1-propanol–water (4:1:2, upper phase). After about 4 hr the solution was treated with Dowex 50 (H^+) (~1 g). Evaporation of the solvent to dryness afforded a foam which crystallized upon addition of methanol (0.4 g, 80%). A small portion was recrystallized from ethanol to give colorless crystals: mp 172–174°; $[\alpha]^{22}D$ −59.5° (*c* 1.0, DMF); λ_{max}^{MeOH} 282 nm (ε 5500), $\lambda_{max}^{pH\ 1}$ 282 nm (ε 5900), $\lambda_{max}^{pH\ 11}$ 321 nm (ε 6400); nmr δ 10.77 (1, broad s, N^3H), 8.31 and 8.03 (2, broad s, $CONH_2$), 6.48 (1, d, H-1′, $J_{1',2'}$ = 7 Hz), 5.45–5.05 (2, m, 5′-OH), 4.00–4.50 (3, m, H-2′, H-3′, H-4′), 3.65 (2, broad s, H-5′, H-5″).

Anal. Calcd for $C_{10}H_{13}O_7N_3$: C, 41.81; H, 4.56; N, 14.64. Found: C, 42.02; H, 4.62; N, 14.42.

Registry No.—**2**, 33780-80-2; **3a**, 33780-81-3; **3b**, 33780-82-4; **4**, 33886-19-0; **5a**, 33886-20-3; **5b**, 33872-65-0; **6**, 33886-21-4; **7**, 33780-83-5; **8**, 33886-22-5; **9**, 33886-23-6; **10**, 33780-84-6; **11**, 33886-24-7.

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Mesoionic Compounds. XVI. 1,4-Dipolar Type Cycloaddition Reactions Utilizing Pyrimidinium Betaines[1]

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N,N′-Disubstituted amidines and carbon suboxide gave in excellent yield *anhydro*-4-hydroxy-6-oxo-1,2,3-trisubstituted pyrimidinium hydroxides which underwent 1,4-dipolar type cycloadditions with dimethyl acetylenedicarboxylate. In the case of *anhydro*-1,3-diphenyl-4-hydroxy-2-methyl-6-oxopyrimidinium hydroxide, the primary adduct, dimethyl 2,6-diaza-3,5-dioxo-2,6-diphenyl-1-methylbicyclo[2.2.2]oct-7-ene-7,8-dicarboxylate, was isolated; on heating, it lost phenyl isocyanate, forming dimethyl 6-methyl-2-oxo-1-phenylpyridine-4,5-dicarboxylate.

1,3-Dipolar cycloaddition reactions utilizing mesoionic ring systems as the source of the 1,3-dipole are well documented in the literature.[2] Both five-membered[2] and six-membered[3] ring systems have been utilized in these reactions. In most instances during the reaction the primary cycloadduct readily lost species such as carbon dioxide,[4] carbonyl sulfide,[5] isocyanates,[6,7] or sulfur[7] leading to substituted heterocycles often difficult to obtain by alternative routes. In other cases the primary cycloadduct was quite stable but, by standard procedures, could be converted into interesting ring systems.[3b,8]

In a recent communication[9] we showed how *anhydro*-

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(2) Summaries of this general area may be found in M. Ohta and H. Kato, "Non Benzenoid Aromatics," J. P. Snyder, Ed., Academic Press, New York, N. Y., 1969, Chapter 4; R. Huisgen, "Aromaticity," Chemical Society Special Publication No. 21, p 51.

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TABLE I

CHEMICAL SHIFTS OF SOME PYRIMIDINE BETAINES (2)[a]

Compd	Solvent[b]	$\tau_{C_6H_5}$	τ_{C_5H}	τ_{CH_3}
$R^1 = R^2 = Ph$	A	2.50–3.13 (m)	5.01 (s)	
	B	2.50–2.9 (d)	3.55 (s, br)	
$R^1 = CH_3$; $R^2 = Ph$	A	2.40–2.96 (m)	5.13 (s)	6.97 (s)
	B	2.35–2.85 (d)	3.47 (s, br)	6.30 (s)
$R^1 = Ph$; $R^2 = CH_3$	A	2.25–2.78 (s, br)	5.21 (s)	8.1 (s)
	B	2.15–2.80 (m)	3.62 (s, br)	7.61 (s)

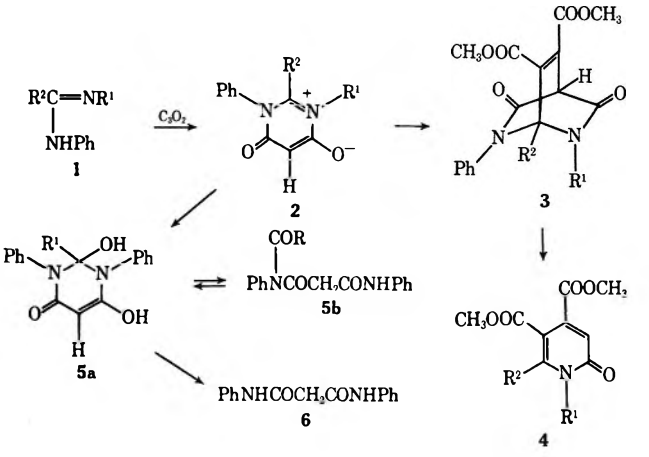
[a] In parts per million from internal TMS. [b] A = DMSO-d_6, B = CF_3COOH.

2-hydroxy-1-methyl-4-oxopyrido[1,2-*a*]pyrimidinium hydroxide underwent a ready cycloaddition reaction with acetylenic dipolarophiles to yield 1,2-disubstituted 4*H*-quinolizin-4-ones, with extrusion of methyl isocyanate. In contrast to the reactions of the six-membered ring systems already reported, this cycloaddition may be interpreted in terms of the intermediacy of a 1,4-dipole.[10] This present communication describes the extension of this concept to a series of pyrimidinium betaines.

The betaines (2) were synthesized in excellent yields by condensation of the *N*,*N*′-disubstituted amidines (1) with carbon suboxide. They were characterized by analytical and spectral data, especially by the presence of molecular ions in their mass spectra and by two carbonyl absorptions at *ca.* 1700 and 1665 cm^{-1}. Hydrolysis experiments also supported the assigned structures. *anhydro*-4-Hydroxy-6-oxo-1,2,3-triphenylpyrimidinium hydroxide (2, $R^1 = R^2 = Ph$), when treated with 2% sodium hydroxide at room temperature for 1 min, gave 2,4-dihydroxy-6-oxo-1,2,3-triphenyl-1,2,3,6-tetrahydropyrimidine (**5a**, $R^1 = Ph$) which, in this case, existed in the carbinolamine form rather than the open chain amino aldehyde form (**5b**). Infrared absorptions (ν_{OH} 3280, ν_{CO} 1698, 1652 cm^{-1}) together with nmr data showing two exchangeable protons (D_2O) at $-\tau$ 0.2, an exchangeable singlet at τ 4.2, and the absence of a methylene group, support structure **5a**. Replacement of the 2-phenyl substituent in 2 with a hydrogen atom greatly increased the susceptibility of the ring system to hydrolysis. *anhydro*-1,3-Diphenyl-4-hydroxy-6-oxopyrimidinium hydroxide (2, $R^1 = Ph$; $R^2 = H$), on dissolution in acetonitrile containing small amounts of water, gave *N*-formylmalonanilide (**5b**, R = H). The existence of the hydrolysis product in this case in the amino aldehyde form was indicated by the spectral data (ν_{NH} 3300, 3200; ν_{CO} 1695, 1655; ν_{CHO} 1725 cm^{-1}), particularly the nmr data, which showed absorptions at τ 6.65 (s, 2, $COCH_2CO$, exchanged with D_2O), 1.56 (broad s, 1, NH, exchanged with D_2O), 0.5 (s, 1, CHO), and aromatic protons. When 2 ($R^1 = Ph$; $R^2 = H$) was heated in aqueous acetone hydrolysis was complete, the product isolated being malonanilide (**6**) which was also obtained from 2 ($R^1 = R^2 = Ph$) and warm sodium hydroxide solution. Reaction of aniline with carbon suboxide gave **6**, whose physical constants were identical with those already described.[11]

Table I lists the nmr data for the pyrimidinium betaines and shows that in trifluoroacetic acid they are to a large extent protonated on the exocyclic oxygen atom. In trifluoroacetic acid the proton attached to C-5 of the nucleus, and also the methyl group at C-2, undergo appreciable downfield shifts of *ca.* 1.5 and 0.5 ppm, respectively, from their resonances observed in DMSO-d_6. No OH proton signal was observed due to the rapid exchange with the solvent. The substantial downfield shift of the C_5 H is attributable to an increase in the heteroatom ring current caused by protonation and is analogous to the results observed on protonation of 3-phenylsydnone and its derivatives.[12] In most of the spectra the singlet due to the C-5 methine hydrogen is invariably broadened in trifluoroacetic acid in comparison to that observed in DMSO-d_6.

These pyrimidinium betaines are derivatives of 4,6-dihydroxypyrimidine and several have been prepared[13] from 5-substituted 4,6-dimethoxypyrimidine in poor yield by reaction with methyl iodide in a sealed tube at 120°. Preparation by this route restricts the substituents on the nitrogen atoms to methyl groups and, in contrast to the betaines described in this current study, those betaines unsubstituted in the five position underwent an interesting dimerization involving positions two and five of the nucleus.



The betaines 2 readily underwent 1,4-dipolar type cycloaddition reactions with dimethyl acetylenedicarboxylate. With *anhydro*-4-hydroxy-1,3-diphenyl-2-methyl-6-oxopyrimidinium betaine (2, $R^1 = Ph$; $R^2 = CH_3$), the primary 1:1 adduct dimethyl 2,6-diaza-3,5-dioxo-2,6-diphenyl-1-methylbicyclo[2.2.2]oct-7-ene-7,8-dicarboxylate (**3**, $R^1 = Ph$; $R^2 = CH_3$) was isolated in 94% yield as colorless needles, mp 188–189°. This structural assignment is based on analytical and spectral data, especially infrared absorptions (ν_{COOCH_3} 1720 cm^{-1}, $\nu_{CON<}$ 1690 cm^{-1}) and nmr data [($CDCl_3$) τ 8.82 (s, 3, C_1 CH_3), 6.11 (s, 3, $C_{7(8)}$ $COOCH_3$), 6.09 (s, 3, $C_{8(7)}$ $COOCH_3$), 5.02 (s, 1, C_4 H), 3.0–2.7 (m, 10,

(10) R. Huisgen, "Topics in Heterocyclic Chemistry," R. N. Castle, Ed., Wiley-Interscience, New York, N. Y., 1969, Chapter 8.

(11) M. Freund, *Ber.*, **17**, 133 (1884).

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aromatics] in which the resonance of the C_4 bridgehead proton is consistent with that found in other [2.2.2] bicyclic ring systems.[14] Thermolysis of **3** resulted in elimination of phenyl isocyanate and the formation of dimethyl 6-methyl-2-oxo-1-phenylpyridine-4,5-dicarboxylate (**4**, R^1 = Ph; R^2 = CH_3). With the other betaines **2**, the intermediate **3** was not isolated, the isocyanate being eliminated during the course of the reaction and the pyridone **4** being obtained directly. It is interesting to note that it is phenyl isocyanate which is eliminated in preference to methyl isocyanate from the intermediate adduct **3** when both possibilities are present. Spectral data of the pyridones **4** were consistent with such a representation and dimethyl 1,6-diphenyl-2-oxopyridine-4,5-dicarboxylate (**4**, R^1 = R^2 = Ph) obtained from 2 (R^1 = R^2 = Ph) was identical with a sample prepared from *anhydro*-2,3-diphenyl-4-hydroxythiazolium hydroxide and dimethyl acetylenedicarboxylate.[7]

Ethyl propiolate and *N*,*N*-diethylaminophenylacetylene as well as olefinic dipolarophiles such as dimethyl maleate did not form well-defined products with the pyrimidinium betaines.

Experimental Section[15]

The following preparation illustrates the method used for the synthesis of the pyrimidinium betaines.

***anhydro*-4-Hydroxy-6-oxo-1,2,3-triphenylpyrimidinium Hydroxide** (**2**, R^1 = R^2 = Ph).—*N*,*N*-Diphenylbenzamidine[16] (1.9 g, 0.007 mol), dissolved in anhydrous ether (70 ml) with a catalytic amount of anhydrous $AlCl_3$, was added slowly to a stirred, ethereal solution of carbon suboxide[17] (*ca.* 0.7 g, 0.01 mol). A crystalline product separated toward the end of this addition. After stirring the reaction mixture at room temperature for 12 hr, the product was collected, washed with anhydrous ether, and recrystallized from absolute ethanol, from which it separated as colorless prisms: yield 1.8 g (76%); mp 255–257° dec; ir (KBr) 3060, 3040 (CH), 1700, 1665 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 350–270 nm (plateau), 253 sh (log ϵ 3.96), 235 sh (4.25), 215 (4.62); nmr (DMSO-d_6) τ 5.01 (s, 1, H_5), 3.13–2.50 (m, 15, aromatic); mass spectrum $M^{+\cdot}$, *m*/*e* (rel intensity) 340 (5).

Anal. Calcd for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74; N, 8.23. Found: C, 77.59; H, 4.76; N, 8.23.

***anhydro*-1,2-Diphenyl-4-hydroxy-3-methyl-6-oxopyrimidinium hydroxide** (**2**, R^1 = CH_3; R^2 = Ph) prepared from *N*-methyl-*N*′-phenylbenzamidine[18] separated from ethanol as colorless prisms: mp 206–208° (100%); ir (KBr) 3050, 2950 (CH), 1695, 1670 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 350–275 nm (plateau), 255 (log ϵ 3.39), 217 (4.27); nmr (DMSO-d_6) τ 6.97 (s, 3, NCH_3), 5.13 (s, 1, H_5), 2.96–2.40 (m, 10, aromatic); mass spectrum $M^{+\cdot}$, *m*/*e* (rel intensity) 278 (17).

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.44; H, 5.07; N, 10.06. Found: C, 73.04; H, 5.12; N, 9.93.

***anhydro*-1,3-Diphenyl-4-hydroxy-6-oxopyrimidinium hydroxide** (**2**, R^1 = Ph; R^2 = H) was obtained from *N*,*N*′-diphenylformamidine[19] as colorless, irregular prisms on trituration of the reaction product with anhydrous acetone: mp 193–195° (78%); ir (KBr) 3035 (CH), 1680, 1670 cm^{-1} (CO); $\lambda_{max}^{CH_2Cl_2}$ 360–315 nm (plateau), 280 sh (log ϵ 3.65), 243 (4.36); nmr (DMSO-d_6) τ 5.25 (s, 1, H_5), 2.67–2.55 (broad s, 10, aromatic), 0.68 (s, 1, H_2). Trace amounts of water present in recrystallization solvents caused sufficient hydrolysis to result in incorrect analytical values.

***anhydro*-1,3-Diphenyl-4-hydroxy-2-methyl-6-oxopyrimidinium hydroxide** (**2**, R^1 = Ph; R^2 = CH_3) was prepared from *N*,*N*′-diphenylacetamidine[20] and crystallized from absolute ethanol as colorless prisms: yield 71%; mp 260–261°; ir (KBr) 3045, 3000, 2900 (CH), 1699, 1665 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 370–345 nm (plateau), 252 (log ϵ 3.82), 208 (4.66); nmr (DMSO-d_6) τ 8.1 (s, 3, C_2CH_3), 5.21 (s, 1, H_5), 2.00 (s, 10, aromatics); mass spectrum $M^{+\cdot}$ *m*/*e* (rel intensity) 278 (9).

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.44; H, 5.07; N, 10.06. Found: C, 73.18; H, 4.98; N, 9.73.

Hydrolysis of *anhydro*-1,3-Diphenyl-4-hydroxy-6-oxopyrimidinium Hydroxide (**2**, R^1 = Ph; R^2 = H).—The betaine (0.39 g, 0.001 mol), acetone (10 ml), and H_2O (1 ml) were refluxed for 30 min. The solvent was evaporated *in vacuo* and the residue was recrystallized from ethanol, affording colorless flakes of *N*,*N*′-diphenylmalonamide, mp 223–225° (lit.[11] mp 223–224°) (92%). The mixture melting point with an authentic sample was not depressed and their ir spectra were identical.

Hydrolysis of *anhydro*-4-Hydroxy-6-oxo-1,2,3-triphenylpyrimidinium Hydroxide (**2**, R^1 = R^2 = Ph).—The betaine (0.4 g) was treated with aqueous sodium hydroxide (20 ml of 2% solution) for 1 min. After filtration, the reaction mixture was acidified with dilute HCl and the product which separated was collected and dried. It crystallized from ethanol as colorless prisms of 2,4-dihydroxy-6-oxo-1,2,3-triphenyl-1,2,3,6-tetrahydropyrimidine (**5a**): 84%; mp 208–210°; ir (KBr) 2980 (OH), 3140–3010 (CH), 1698 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 310 nm sh (log ϵ 4.07), 267 sh (4.82), 256 (4.85), 201 (5.06); nmr (DMSO-d_6) τ 4.20 (s, 1, H_5, exchanged with D_2O), 1.9–2.95 (m, 15, aromatic), −0.2 (s, 2, OH, exchanged with D_2O); mass spectrm $M^{+\cdot}$, *m*/*e* (rel intensity) 358 (1).

Anal. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.81; H, 5.05; N, 7.31. Found: C, 73.51; H, 5.07; N, 7.73.

Hydrolysis of *anhydro*-1,3-Diphenyl-4-hydroxy-6-oxopyrimidinium Hydroxide (**2**, R^1 = Ph; R^2 = H).—The above betaine, on dissolution in wet acetonitrile, gave a small amount of *N*-formylmalonanilide (**5b**, R = H) as colorless rhombs: mp 122–123°; ir (KBr) 3300, 3200 (NH), 3150, 3055, 2940 (CH), 1725 (CO), 1695, 1655 cm^{-1} (CON<); nmr ($CDCl_3$) τ 6.65 (s, 2, CH_2, exchanged with D_2O), 2.42–3.00 (m, 10, aromatic), 1.56 (broad s, 1, NH, exchanged with D_2O), 0.5 (s, 1, CHO); mass spectrum, $M^{+\cdot}$, *m*/*e* (rel intensity) 282 (3).

Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.01; H, 5.00; N, 9.93. Found: C, 67.97; H, 4.94; N, 9.86.

Dimethyl 1,6-Diphenyl-2-oxopyridine-4,5-dicarboxylate (**4**, R^1 = R^2 = Ph).—The betaine 2 (R^1 = R^2 = Ph) (0.34 g, 0.001 mol), dimethyl acetylenedicarboxylate (0.568 g, 0.004 mol), and acetone (15 ml) were refluxed for 24 hr. Acetone was then removed *in vacuo* and the residue was chromatographed on silica gel (Fluorsil F-100) with benzene–ether (2:1) as eluent. The product was recrystallized from chloroform–ether, giving colorless prisms, mp 180–182° (82%) (lit.[7] mp 180–181°).

In a similar manner, **dimethyl 1-methyl-2-oxo-6-phenylpyridine-4,5-dicarboxylate** (**4**, R^1 = CH_3; R^2 = Ph) was prepared from 2 (R^1 = CH_3; R^2 = Ph) and dimethyl acetylenedicarboxylate in 55% yield. In this case the reaction mixture was refluxed for 48 hr, chromatographed on silica gel, and eluted with benzene–ether (1:1). The product recrystallized from benzene–petroleum ether (bp 30–60°) forming colorless prisms: mp 102–103°; ir (KBr) 3060, 2950 (CH), 1735, 1650 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 330 nm (log ϵ 3.82), 250 (3.95); nmr ($CDCl_3$) τ 6.77 (s, 3, C_5COOCH_3), 6.57 (s, 3, C_6COOCH_3), 6.15 (s, 3, NCH_3), 2.95 (s, 1, H_3), 2.4–2.85 (m, 5, aromatic); mass spectrum, $M^{+\cdot}$, *m*/*e* (rel intensity) 301 (100).

Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.46; H, 5.02; N, 4.53.

Dimethyl 2,6-Diaza-3,5-dioxo-2,6-diphenyl-1-methylbicyclo-[2.2.2]oct-7-ene-7,8-dicarboxylate (**3**, R^1 = Ph; R^2 = CH_3).—The betaine 2 (R^1 = Ph; R^2 = CH_3) (0.6 g, 0.0022 mol), dimethyl acetylenedicarboxylate (0.612 g, 0.0043 mol), and benzene (50 ml) were refluxed for 24 hr. The solvent was evaporated *in vacuo* and the residue, after trituration with ether, was recrystallized

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(15) Spectral characterization of products was carried out on the following instrumentation: ir, Perkin-Elmer Model 337 spectrophotometer; uv, Cary Model 14 spectrophotometer; nmr, Varian A-60 nmr spectrometer using TMS as internal standard; mass spectra, Hitachi Perkin-Elmer RMU-6E mass spectrometer, 70 eV, using the direct inlet probe at a source of temperature of *ca.* 100°. All evaporations were done under reduced pressure using a rotatory evaporator and melting points were taken in capillaries. Chromatographic columns utilized a length:width ratio of 10:1. Microanalyses were by Instranal Laboratories, Rensselaer, N. Y.

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(19) L. Claisen, *Justus Liebigs Ann. Chem.*, **287**, 366 (1895).

(20) E. Bamberger and J. Lorenzen, *ibid.*, **273**, 300 (1893).

from ethanol, affording colorless needles: mp 188–189° (94%); ir (KBr) 3045, 3010, 2960 (CH), 1720, 1690 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 235 nm sh (log ϵ 3.00), 2.00 (4.69); nmr ($CDCl_3$) τ 8.82 (s, 3, C_1 CH_3), 6.11 (s, 3, C_6 $COOCH_3$), 6.09 (s, 3, C_5 $COOCH_3$), 5.02 (s, 1, H_4), 3.0–2.4 (m, 10, aromatic); mass spectrum, identical with that of **4** (R^1 = Ph; R^2 = CH_3).

Anal. Calcd for $C_{23}H_{20}N_2O_6$: C, 65.70; H, 4.80; N, 6.66. Found: C, 65.62; H, 4.78; N, 6.62.

Thermal Elimination of Phenyl Isocyanate from 3 (R^1 = Ph; R^2 = CH_3).—The primary adduct **3** (R^1 = Ph; R^2 = CH_3) (0.42 g, 0.001 mol) was heated for 20 min above its melting point at about 0.5 mm. After cooling and trituration with ether, the product crystallized from benzene–cyclohexane as colorless prisms of dimethyl 6-methyl-2-oxo-1-phenylpyridine-4,5-dicarboxylate (**4**, R^1 = Ph; R^2 = CH_3): 90%; mp 155–158°; ir (KBr) 3001, 2950 (CH), 1740, 1725, 1660 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 328 nm (log ϵ 3.74), 251 (4.08), 203 (4.68); nmr ($CDCl_3$) τ 7.90 (s, 3, C_6 CH_3), 6.17 (s, 3, C_4 $COOCH_3$), 6.10 (s, 3, C_5 $COOCH_3$), 3.09 (s, 1, H_3), 2.32–2.90 (m, 10, aromatic); mass spectrum, $M^{+\cdot}$, m/e (rel intensity) 301 (100).

Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.50; H, 4.98; N, 4.52.

Registry No.—**2** (R^1 = R^2 = Ph), 33821-84-0; **2** (R^1 = CH_3; R^2 = Ph), 33821-85-1; **2** (R^1 = Ph; R^2 = H), 33821-86-2; **2** (R^1 = Ph; R^2 = CH_3), 33821-87-3; **3** (R^1 = Ph; R^2 = CH_3), 33821-88-4; **4** (R^1 = CH_3; R^2 = Ph), 33821-89-5; **4** (R^1 = Ph; R^2 = CH_3), 33821-90-8; **5a** (R^1 = Ph), 33821-91-9; **5b** (R = H), 33821-92-0.

Liquid Crystals. II. Unsymmetrical *p*-Phenylene Di-*p*-*n*-alkoxybenzoates[1]

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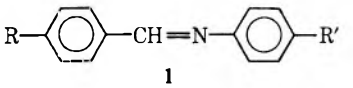
Nematic mesophases that exist at low temperatures are desirable in several applications, but compounds which exhibit nematic mesomorphism tend also to have high melting points. Schiff bases (**1**), the best materials for these applications until recently, are relatively unstable chemically. Esters are more stable and the symmetrical *p*-phenylene di-*p*-*n*-alkoxybenzoates (**2**, R = R′) are nematogenic. However, no compound in this series melts to a nematic mesophase below 122°. The possibility of obtaining lower melting nematic esters by introducing molecular dissymmetry was explored. Twenty-eight unsymmetrical esters (**2**, R ≠ R′), providing all possible combinations of terminal *n*-alkyl groups from methyl through *n*-octyl, were synthesized and their phase transition temperatures determined. The nematic–isotropic transition point is high, even for the most unsymmetrical esters, while the melting point is depressed. The lowest melting products are the hexyl–octyl and pentyl–heptyl esters, which are nematic at 107–202 and 108–210°, respectively. The high nematic–isotropic transition temperatures of these compounds suggest that much lower melting points can be achieved in this system, without losing nematic mesomorphism, by introducing even more molecular dissymmetry. In addition to the 28 unsymmetrical esters of type **2**, seven new *p*-hydroxyphenyl *p*-*n*-alkoxybenzoates (**3**) and the previously unreported **2** (R = R′ = n-C_5H_{11}) were also prepared. Similar studies of other chemically stable nematic compounds are reviewed briefly.

Nematic liquid crystallinity (mesomorphism)[2,3] is exhibited by certain compounds with relatively rigid, polar, rod-shaped molecules that tend to be oriented with their long axes parallel because of mutual attractive forces. When such a compound is heated, the crystalline solid melts to a birefringent, anisotropic liquid (nematic mesophase) in which adjoining molecules lie parallel to one another. At a higher temperature, the mesophase undergoes transition to isotropic liquid.

For practical applications, such as optical and display devices[4] and gas–liquid chromatography,[5] nematic mesophases which exist at or near room temperature are desirable. This is a difficult criterion to meet because the molecular characteristics that are necessary for nematic mesomorphism also produce stable crystalline lattices. Accordingly, nematic compounds generally have high melting points. Success in meeting the requirement has been achieved with nematic substances having a relatively high degree of molecular dissymmetry and their mixtures. The dissymmetry and the mixing depress the solid–nematic melting point without necessarily lowering the nematic–isotopic transition temperature. Accordingly, by proper selection of compounds, low melting points are obtainable with retention of nematic mesomorphism.

At the time our investigation was begun, the outstanding examples of these successes involved Schiff bases (**1**). A ternary mixture of **1** (R = CH_3O; R′ = n-C_3H_7COO), **1** (R = n-C_4H_9O; R′ = CH_3COO), and **1** (R = CH_3O; R′ = CH_3COO) has a nematic range[6] of 22–105°.[7] The compound **1** (R = CH_3O; R′ = n-C_4H_9) is nematic at 22–48°.[8] The trouble with Schiff bases is their hydrolytic, oxidative, and thermal instability. Aromatic esters are much more stable, and symmetrical *p*-phenylene di-*p*-*n*-alkoxybenzoates (**2**, R = R′) are known to have long nematic ranges.[9,10] However, no compound in the series undergoes transi-



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(1) (a) Presented at the 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971. (b) From the M.S. thesis of S. A. H., The University of North Carolina at Greensboro, 1971. (c) This work was supported in part by a grant-in-aid from The University of North Carolina at Greensboro Research Council. (d) Previous paper in this series: J. P. Schroeder and Dorothy C. Schroeder, *J. Org. Chem.*, **33**, 591 (1968).

(2) G. W. Gray, "Molecular Structure and the Properties of Liquid Crystals," Academic Press, New York, N. Y., 1962.

(3) G. H. Brown and W. G. Shaw, *Chem. Rev.*, **57**, 1049 (1957).

(4) T. Kallard, Ed., "Liquid Crystals and Their Applications," Optosonic Press, New York, N. Y., 1970.

(5) H. Kelker and E. Von-Schivizhoffen, *Advan. Chromatog.*, **6**, 247 (1968).

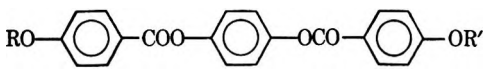
(6) Temperature range over which the nematic mesophase exists.

(7) J. E. Goldmacher and J. A. Castellano (to Radio Corporation of America), British Patent 1,170,486 (Nov. 12, 1969).

(8) (a) H. Kelker and B. Scheurle, *Angew. Chem., Int. Ed. Engl.*, **8**, 884 (1969); (b) H. Kelker, B. Scheurle, R. Hatz, and W. Bartsch, *ibid.*, **9**, 962 (1970).

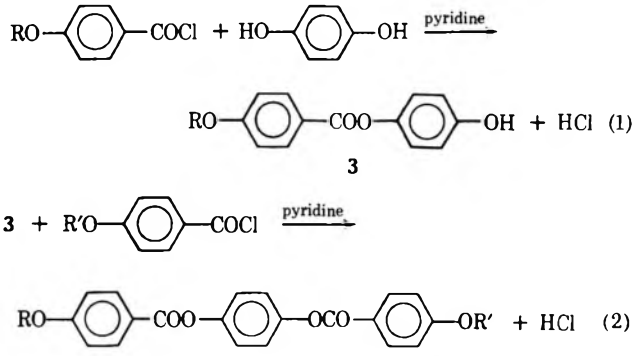
(9) M. J. S. Dewar and J. P. Schroeder, *J. Org. Chem.*, **30**, 2296 (1965).

(10) S. L. Arora, J. L. Fergason, and T. R. Taylor, *ibid.*, **35**, 4055 (1970).



2

tion to the nematic mesophase below 122°. This paper describes an exploration of the molecular dissymmetry approach to low melting nematic compounds based on this chemically more stable system. Twenty-eight esters of type 2 ($R \neq R'$) were synthesized, encompassing all combinations of the terminal *n*-alkoxy groups CH_3O through *n*-$C_8H_{17}O$. The experimental procedure was to prepare a *p*-hydroxyphenyl *p*-*n*-alkoxybenzoate (3) from a *p*-alkoxybenzoyl chloride and an excess of hydroquinone in pyridine solution (eq 1). This was converted to the desired unsymmetrical diester by reaction with a different *p*-alkoxybenzoyl chloride, again in pyridine (eq 2). In the



course of the study, 7 new compounds of type 3 and the previously unreported 2 ($R = R' = n\text{-}C_5H_{11}$) were also prepared. The phase transition temperatures of these materials were determined using a hot stage polarizing microscope.

While this study was in progress, several reports of similar approaches were published. It was shown[10] that molecular dissymmetry in esters of type 2 ($R = R'$) resulting from introduction of a methyl substituent on the central phenylene group shifts the nematic range downward significantly. *E.g.*, the methyl-substituted ester with $R = R' = n\text{-}C_8H_{17}$ is nematic at 72–156° as compared with 126–195° for 2 ($R = R' = n\text{-}C_8H_{17}$). Another unsymmetrical ester system that has been studied is the homologous series of *p*-alkoxyphenyl *p*-alkylcarbonatobenzoates.[11] Mixtures of these compounds have solid–nematic transition temperatures as low as 24°. Additional chemically stable systems that exhibit nematic mesophases at low temperatures are unsymmetrically substituted azoxybenzenes,[8b,12,13] stilbenes,[14] and tolanes.[15]

Experimental Section

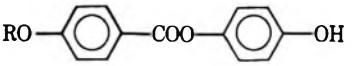
***p*-*n*-Alkoxybenzoic Acids.**—The ethoxy, butyloxy, and octyloxy acids were commercial products. The others were obtained by reaction of ethyl *p*-hydroxybenzoate with the appropriate *n*-alkyl bromides and saponification of the resulting ethyl *p*-alkoxybenzoates in ethanolic KOH solution.[9] The products had the following phase transitions: *p*-*n*-propyloxybenzoic acid, solid–nematic at 145°, nematic–isotropic at 156° (lit.[16] 145, 154°); *p*-*n*-hexyloxybenzoic acid, solid–nematic at 109°, nematic–isotropic at 155° (lit.[16] 105, 153°); *p*-*n*-heptyloxybenzoic acid, solid–smectic at 94°, smectic–nematic at 99°, nematic–isotropic at 146° (lit.[16] 92, 98, 146°).

***p*-*n*-Alkoxybenzoyl Chlorides.**—The methoxy and pentyloxy compounds were purchased. The others were prepared from the corresponding acids by treatment with thionyl chloride in the presence of pyridine as catalyst. Excess thionyl chloride was distilled to give the acid chlorides as residue products.

***p*-Hydroxyphenyl *p*-*n*-Alkoxybenzoates (3).**—Typically, 0.10 mol of the appropriate *p*-*n*-alkoxybenzoyl chloride was added with stirring to a saturated solution of hydroquinone (0.50 mol) in dry pyridine. After stirring for 20–24 hr, the mixture was poured into 1.1 l. of 2.2 *N* hydrochloric acid. The precipitated solid was collected by filtration, washed with water, and stirred for 1 hr in 1 l. of saturated aqueous $NaHCO_3$ solution to remove any *p*-alkoxybenzoic acid from unreacted acid chloride. The slurry was filtered to recover the desired hydroxyphenyl ester.[17] After this was washed with water, the solid was dried at 100° and used in the next step without further purification.[18] The crude yields and the melting points and analyses of the materials after recrystallization from ethanol–water are listed in Table I.

TABLE I

p-HYDROXYPHENYL *p*-*n*-ALKOXYBENZOATES[a]



R	Registry no.	Yield, %	Mp, °C	% C Calcd	% C Found	% H Calcd	% H Found
CH_3		84	156[b]				
C_2H_5	33905-60-1	89	164	69.8	69.75	5.5	5.1
$n\text{-}C_3H_7$	33905-61-2	90	136	70.6	70.75	5.9	6.1
$n\text{-}C_4H_9$	33905-62-3	88	144	71.3	71.55	6.3	6.6
$n\text{-}C_5H_{11}$	33905-63-4	80	120	72.0	71.7	6.7	6.5
$n\text{-}C_6H_{13}$	33905-64-5	66	116	72.6	72.5	7.05	6.9
$n\text{-}C_7H_{15}$	33905-65-6	86	113	73.15	73.2	7.4	7.4
$n\text{-}C_8H_{17}$	33905-66-7	85	111	73.7	73.3	7.65	7.3

[a] Satisfactory analytical data (±0.4% for C and H) were reported for all new compounds listed in the table: Ed. [b] Literature mp 152°: M. J. S. Dewar and R. S. Goldberg, *J. Amer. Chem. Soc.*, 92, 1582 (1970).

***p*-Phenylene Di-*p*-*n*-alkoxybenzoates (2).**—The unsymmetrical esters were synthesized from the appropriate *p*-*n*-alkoxybenzoyl chloride and hydroxyphenyl *p*-*n*-alkoxybenzoate by essentially the same procedure used to prepare the latter except that, at the start, a solution of the phenol was added to a solution of the acid chloride (3 mol/mol of phenol), both in anhydrous pyridine. The dried product was dissolved in a suitable solvent, treated with Norit, and recrystallized twice from that solvent and then repeatedly from a mixture of the same solvent and hexane until the phase transition temperatures remained constant. *p*-Phenylene di-*p*-*n*-pentyloxybenzoate was prepared by the reaction of excess *p*-*n*-pentyloxybenzoyl chloride and hydroquinone in dry pyridine.[9]

The results are summarized in Table II along with the transition temperatures of symmetrical esters from the literature for comparison.

Transition Temperatures.—These were determined with a Reichert "Thermopan" polarizing microscope equipped with a Kofler micro hot stage. The instrument was calibrated against pure compounds of known melting points.

Analyses.—The elemental microanalyses were performed by Dr. Kurt Eder, Laboratoire Microchimique, Ecole de Chimie, Geneva, Switzerland.

(11) M. T. McCaffrey, J. E. Goldmacher, and J. A. Castellano, *Mol. Cryst. Liq. Cryst.*, **12**, 345 (1971).

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(13) M. T. McCaffrey and J. A. Castellano, Abstracts, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, PHYS Paper No. 148.

(14) W. R. Young, A. Aviram, and R. J. Cox, *Angew. Chem., Int. Ed. Engl.*, **10**, 410 (1971); Abstracts, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, PHYS Paper No. 147.

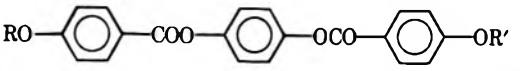
(15) J. Malthete, M. Leclercq, J. Gabard, J. Billard, and J. Jacques, *C. R. Acad. Sci., Paris, Ser. C*, **273**, 265 (1971).

(16) G. W. Gray and B. Jones, *J. Chem. Soc.*, 4179 (1953).

(17) The heptyloxy and octyloxy products required hot filtration because of the low water solubility of the sodium *p*-alkoxybenzoate at room temperature.

(18) Recrystallization of the intermediate before the next step is recommended. Despite the large excess of hydroquinone in the reaction, some symmetrical ester was usually produced and this was troublesome to remove from the unsymmetrical ester.

TABLE II
p-PHENYLENE DI-*p*-*n*-ALKOXYBENZOATES[a]



R	R'	Registry no..	Recrystn solvent	Yield, %	Nematic range, °C	% C Calcd	% C Found	% H Calcd	% H Found
CH_3	CH_3				222–300[b]				
CH_3	C_2H_5	33905-67-8	Dioxane	81	213–295	70.4	70.1	5.1	5.3
CH_3	n-C_3H_7	33905-68-9	Dioxane	67	167–277	70.9	70.7	5.5	5.25
CH_3	n-C_4H_9	33905-69-0	EtOAc	75	134–266	71.4	71.8	5.75	5.8
CH_3	n-C_5H_{11}	33905-70-3	Dioxane	56	137–253	71.9	72.1	6.0	6.0
CH_3	n-C_6H_{13}	33905-71-4	EtOAc	54	125–244	72.3	72.4	6.3	6.3
CH_3	n-C_7H_{15}	33905-72-5	EtOAc	66	127–234	72.7	72.5	6.5	6.4
CH_3	n-C_8H_{17}	33905-73-6	EtOAc	62	125–229	73.1	73.25	6.8	6.5
C_2H_5	C_2H_5				226–287[c]				
C_2H_5	n-C_3H_7	33905-74-7	Dioxane	81	198–278	71.4	70.9	5.75	5.8
C_2H_5	n-C_4H_9	33905-75-8	Dioxane	77	150–270	71.9	71.6	6.0	6.2
C_2H_5	n-C_5H_{11}	33905-76-9	Dioxane	69	150–251	72.3	72.5	6.3	6.3
C_2H_5	n-C_6H_{13}	33905-77-0	EtOAc	81	134–248	72.7	72.1	6.5	6.2
C_2H_5	n-C_7H_{15}	33905-78-1	EtOAc	84	130–235	73.1	73.5	6.8	6.7
C_2H_5	n-C_8H_{17}	33905-79-2	EtOAc	74	124–235	73.45	73.5	7.0	6.8
n-C_3H_7	n-C_3H_7				175–249[c]				
n-C_3H_7	n-C_4H_9	33905-80-5	EtOAc	82	151–248	72.3	72.2	6.3	6.5
n-C_3H_7	n-C_5H_{11}	33905-81-6	EtOAc	59	126–236	72.7	72.8	6.5	6.9
n-C_3H_7	n-C_6H_{13}	33905-82-7	EtOAc	78	114–230	73.1	73.2	6.8	7.0
n-C_3H_7	n-C_7H_{15}	33905-83-8	EtOAc	67	120–222	73.45	73.3	7.0	7.2
n-C_3H_7	n-C_8H_{17}	33966-22-2	EtOAc	71	128–216	73.8	74.2	7.2	7.25
n-C_4H_9	n-C_4H_9				153–241[c]				
n-C_4H_9	n-C_5H_{11}	33903-88-7	EtOAc	75	140–229	73.1	73.7	6.8	6.8
n-C_4H_9	n-C_6H_{13}	33903-89-8	EtOAc	75	117–226	73.45	73.7	7.0	7.05
n-C_4H_9	n-C_7H_{15}	33903-90-1	EtOAc	67	114–218	73.8	74.0	7.2	7.3
n-C_4H_9	n-C_8H_{17}	33903-91-2	EtOAc	72	121–214	74.1	73.9	7.4	7.3
n-C_5H_{11}	n-C_5H_{11}	33903-92-3	EtOAc	78	145–222	73.45	73.4	7.0	7.2
n-C_5H_{11}	n-C_6H_{13}	33903-93-4	EtOAc	62	123–215	73.8	73.3	7.2	7.1
n-C_5H_{11}	n-C_7H_{15}	33903-94-5	EtOAc	69	108–210	74.1	74.1	7.4	7.2
n-C_5H_{11}	n-C_8H_{17}	33903-95-6	EtOAc	74	116–207	74.4	74.4	7.6	7.6
n-C_6H_{13}	n-C_6H_{13}				124–213[d]				
n-C_6H_{13}	n-C_7H_{15}	33903-96-7	Hexane	74	118–206	74.4	74.2	7.6	7.5
n-C_6H_{13}	n-C_8H_{17}	33903-97-8	Hexane	66	107–202[e]	74.7	74.2	7.7	7.8
n-C_7H_{15}	n-C_7H_{15}	1819-00-7			122–199[d,f]				
n-C_7H_{15}	n-C_8H_{17}	33903-99-0	Hexane	57	121–198[g]	75.0	74.8	7.9	7.6
n-C_8H_{17}	n-C_8H_{17}				126–195[d,h]				

[a] Satisfactory analytical data (±0.4% for C and H) were reported for all new compounds listed in the table with some exceptions: Ed. These follow for per cent carbon calculated and found (R, R'): 71.4 and 70.9 (C_2H_5, n-C_3H_7); 72.7 and 72.1 (C_2H_5, n-C_6H_{13}); 73.1 and 73.7 (n-C_4H_9, n-C_5H_{11}); 73.8 and 73.3 (n-C_5H_{11}, n-C_6H_{13}); 74.7 and 74.2 (n-C_6H_{13}, n-C_8H_{17}). [b] Reference 9. [c] M. J. S. Dewar and R. S. Goldberg, *J. Org. Chem.*, **35**, 2711 (1970); reference in footnote *b*, Table I. [d] Reference 10. [e] Smectic range 106–107°. [f] Monotropic nematic–smectic transition at 110°. [g] Smectic range 114–121°. [h] Smectic range 122–126°.

Results and Discussion

The data from Table II are presented graphically in Figures 1 and 2. Figure 1 shows the effect on the nematic–isotropic (N–I) transition temperatures of *p*-phenylene di-*p*-*n*-alkoxybenzoates produced by varying one terminal *n*-alkyl group while holding the other constant. Figure 2 treats the melting points and smectic–nematic transition temperatures[19] in the same manner. Because of congestion of data points and intersections of curves, Figure 2 is divided into two parts with the plots for the C_1 through C_4 esters above and those for the C_5 through C_8 esters below.

In Figure 1, there is a rather regular drop in N–I transition temperature with increasing length of the varied *n*-alkyl group for all curves. This is consistent with results for other homologous series and reflects the decreasing thermal stability of the nematic mesophase with decreasing molecular rigidity and polarity (increasing *n*-alkane character).[2] For the same reason, the curves lie at progressively lower temperatures as the length of the constant alkyl group increases. This is not a regular progression, however. The curves are grouped in pairs (C_1–C_2, C_3–C_4, C_5–C_6, C_7–C_8), suggesting that there is, *e.g.*, very little difference in disruptive effect on the mesophase between CH_3 and C_2H_5, and between n-C_3H_7 and n-C_4H_9, but the latter two groups have a significantly greater effect than the former. The drop in N–I transition point on traversing a curve from the CH_3 to the n-C_8H_{17} homolog varies from 71° for the C_1 series to 34° for the C_8 series. Both the N–I transition temperatures and the melting points (Figure 2) of the ethyl homologs are generally higher than would be expected from interpolation based on the other data points. This recalls the homologous series of 4,4'-di-*n*-alkoxyazoxybenzenes in which the ethyl compound has the highest melting and N–I transition temperatures.[20,21]

(19) For a discussion of smectic mesophases, see A. Saupe, *Mol. Cryst. Liq. Cryst.*, **7**, 59 (1969).

(20) W. Maier and G. Englert, *Z. Phys. Chem. (Frankfurt)*, **19**, 168 (1959).

(21) C. Weygand and R. Gabler, *J. Prakt. Chem.*, **155**, 332 (1940).

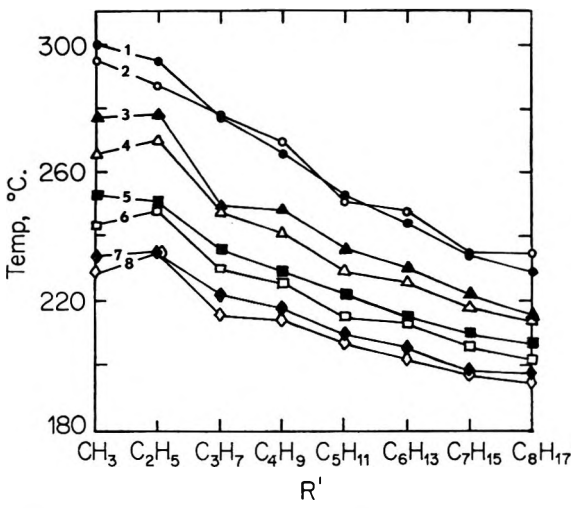


Figure 1.—Nematic-isotropic transition temperatures of *p*-phenylene di-*p*-*n*-alkoxybenzoates (**2**). For each curve, R is constant (R = CH_3 for curve 1, C_2H_5 for curve 2, etc.) while R′ is varied from CH_3 through *n*-C_8H_{17}.

The melting point curves (Figure 2) are much less regular than those for the N–I transitions, being strongly influenced by molecular symmetry and by the ethyl group effect just described. Good examples of this are the C_4 and C_5 curves. Traversing the former from left to right, the melting point rises on going from the methyl to the ethyl homolog and then remains almost constant through the pentyl compound before dropping off as dissymmetry and increasing alkane character exert their effects. In the C_5 curve, there are two obvious maxima at the ethyl and symmetrical pentyl homologs. The C_1, C_2, and C_3 curves decline steeply between the ethyl and butyl to hexyl homologs as dissymmetry and alkane character increase. The melting point of the CH_3–*n*-C_4H_9 ester is 88° below that of the CH_3–CH_3 ester (134 *vs.* 222°). The right-hand portions of these curves and the entire curves for the C_6, C_7, and C_8 series are fairly level, reflecting the dominant effect of the long alkyl chains. However, the influences of symmetry and the ethyl group can still be detected. Smectic mesomorphism appears only in the C_6, C_7, and C_8 series.

The data show that the introduction of dissymmetry produces the expected melting point depression without lowering the N–I transition temperature drastically (198° minimum). The lowest temperatures of transition to nematic liquid are 107 and 108°, *i.e.*, 14–15° below the lowest value for the symmetrical ester series. The new materials are still too high melting to be of practical interest, but they show promise. Their high N–I transition temperatures suggest that this chemically stable system would tolerate much more molecular dissymmetry without losing its nematic mesomorphism. Highly asymmetric esters and their mixtures should exhibit markedly lower melting points. Work along this line is in progress.

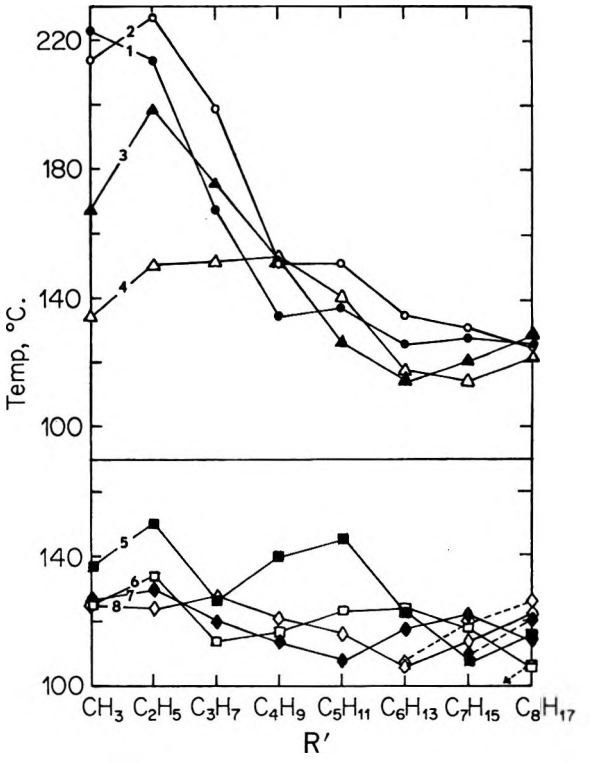


Figure 2.—Melting points and smectic–nematic transition temperatures of *p*-phenylene di-*p*-*n*-alkoxybenzoates (**2**). For each melting point curve, R is constant (R = CH_3 for curve 1, C_2H_5 for curve 2, etc.) while R′ is varied from CH_3 through *n*-C_8H_{17}. Smectic–nematic transition temperatures are indicated by the same symbols, but are connected by dotted, rather than solid, lines.

Methylene Blue Photosensitized Conversion of 3-Substituted Indoles to β-Carboline Derivatives

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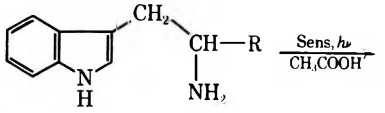
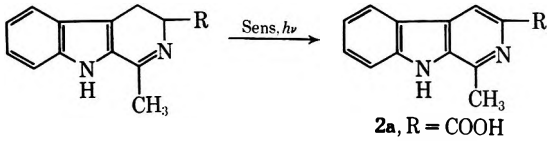
Indole derivatives substituted in the 3 position with a side chain bearing a free β-amino group undergo facile conversion to β-carbolines when a solution of the indole in a carboxylic acid is irradiated with visible light in the presence of methylene blue as the sensitizer. β-Carbolines variously substituted in the 1 and 3 position can be obtained by an appropriate choice of the solvent and indole side chain. The photoreaction appears to proceed through ·OH abstraction from the solvent molecule by photoexcited methylene blue, with formation of an acyl $R\dot{C}{=}O$ radical, which attacks the 2 position of the indole substrate. The 2-acyl derivative thus obtained undergoes a dark cyclization to β-carboline by a Schiff base formation between the carbonyl function and the side chain amino group. Finally, the dihydro-β-carboline is aromatized by methylene blue photosensitized dehydrogenation.

A previous note from this laboratory[1] described a novel photoreaction of tryptophan (**1a**), leading to the formation of β-carboline derivatives by irradiation of the amino acid with visible light in acetic acid solution and in the presence of methylene blue as the sensitizer. The reaction was found to proceed through a dihydro intermediate according to the following scheme.



1a, R = COOH
b, R = H
c, R = $COOC_2H_5$
d, R = CH_2OH
e, R = $CONH_2$



2a, R = COOH
b, R = H
c, R = $COOC_2H_5$
d, R = CH_2OH
e, R = $CONH_2$

By this photoprocess, high yields of 1-methyl-3-carboxy-β-carboline (**2a**) could be easily obtained, whereas the chemical synthesis of this and analogous compounds usually involves complex procedures, yielding relatively low amounts of the desired products.[2-4]

Owing to the importance of β-carbolines in the field of indole alkaloids, it appeared of interest to investigate the preparative and mechanistic features of the aforesaid photoreaction in greater detail. Moreover, on the basis of the reaction scheme outlined above, we explored the possibility of synthesizing differently substituted β-carbolines by changing the type of the solvent, as well as the nature of the side chain in the 3 position of the indole ring.

(1) G. Jori, G. Galiazzo, and G. Gennari, *Photochem. Photobiol.*, **9**, 179 (1969).
(2) R. Tschesche and H. Jenssen, *Chem. Ber.*, **93**, 271 (1960).
(3) H. R. Snyder, C. H. Hansch, L. Katz, S. M. Parmeter, and E. C. Spaeth, *J. Amer. Chem. Soc.*, **70**, 219 (1948).
(4) I. S. Spenser, *Can. J. Chem.*, **37**, 1851 (1959).

Results and Discussion

Irradiation of 3-Substituted Indoles in Acetic Acid Solutions.—The irradiation of the 3-substituted indoles listed in Table I, in either oxygen-saturated or deaerated acetic solutions, caused a gradual disappearance of the starting material, as determined by paper or thin layer chromatography. Concomitantly, new spots were detected which displayed a deep blue fluorescence under 254-mμ light and gave negative color tests with ninhydrin and with Ehrlich's reagent.[5] This strongly suggested that both the side chain amino group and the 2 position of the indole ring were masked as a consequence of the photoreaction. By analogy with our previous findings about the photocyclode hydrogenation process, which **1a** underwent when irradiated under the same conditions,[1] we inferred that the fluorescent products were β-carboline derivatives. This assignment was fully supported by elemental analysis and by spectroscopic characterization of the purified reaction products (see Experimental Section).

TABLE I
FORMATION OF β-CARBOLINES FROM IRRADIATED 3-SUBSTITUTED INDOLES[a]

Substrate	Product(s) obtained	Yield in the aerated solution, %	Yield in the deaerated solution, %
1a	**2a, 2b**	63, 16[b]	71, 24
1b	**2b**	75	93
1c	**2c**	75	95
1d	**2d**	69	87
1e	**2e**	65	88

[a] The irradiations were carried out at 25°, in acetic acid solution and in the presence of methylene blue as the sensitizer, using four 300-W tungsten lamps as the light source. The yields were calculated for the crystallized products. [b] Taken from ref 1.

It is noteworthy that, as shown in Table I, the yield of β-carbolines was enhanced by performing the irradiation in deaerated solutions. Since the primary step in the formation of β-carbolines involves the interaction between the solvent molecules and the triplet sensitizer (see later), the lower yields obtained upon irradiation in O_2-saturated solutions are probably due to the competition of molecular oxygen with acetic

(5) E. Stahl in "Dünnschicht Chromatographie," Springer-Verlag, West Berlin, 1962, p 503.

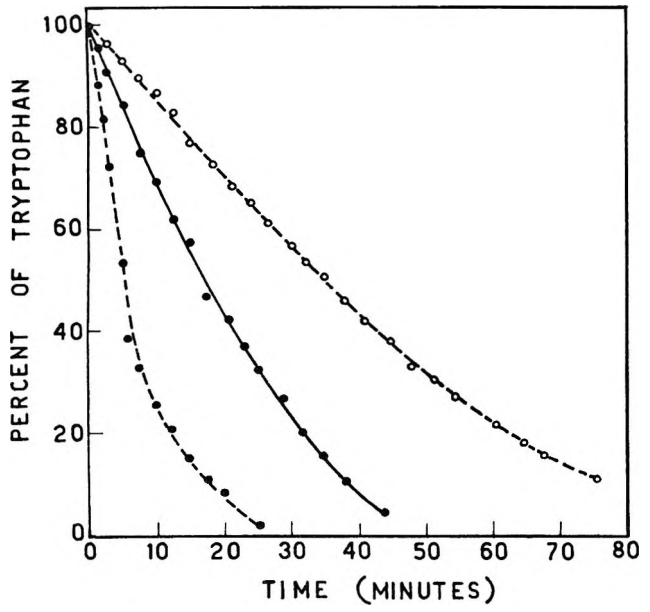


Figure 1.—The time course of tryptophan disappearance upon irradiation at 20° of a 1 m*M* deaerated solution of the amino acid in acetic acid (O---O), isobutyric acid (●—●), and pivalic acid (●- - -●), and in the presence of equimolar methylene blue as the photosensitizer. The plot obtained upon irradiation in propionic acid solution was closely similar to that shown for acetic acid.

acid for the photoexcited methylene blue. Actually, all the indole derivatives examined, when irradiated in the presence of O_2, gave appreciable amounts of insoluble material, which appeared by chromatographic and colorimetric analysis to be composed mainly of melanines of indole structure.[6] These compounds are known to be produced by photosensitized oxygenation of **1a**.[7]

The lack of side products when the photoreaction is carried out under nitrogen simplifies the experimental procedure for the isolation and purification of β-carbolines and renders this novel preparative approach even more valuable. It is apparent that the requirements to be fulfilled by the side chain for the cyclization to occur are the presence of two carbon atoms and of a free terminal amino group.[8] On the other hand, the yield of β-carbolines is practically independent of the type of the second substituent eventually present on the carbon bearing the NH_2 group (see Table I). This fact opens large possibilities of preparing new β-carbolines; for example, as far as we know, compounds **2d** and **2e** have not been isolated up to now. Moreover, the partial photolytic decarboxylation, which occurs when tryptophan is the starting material,[1] can be avoided by irradiation of tryptophan ethyl ester; the free 3-carboxy-β-carboline can be easily obtained by saponification of **2c**.

The decarboxylated product (**2b**) is quantitatively formed by irradiation of tryptamine.

Irradiation of Tryptophan in Other Acid Organic Solvents.—Changing the length and the branching of the hydrocarbon chain of the organic acid used as the solvent had no marked effect on the yield of the corresponding 1-alkyl-3-carboxy-β-carbolines (Table II).

(6) R. A. Nicolaus, *Gazz. Chim. Ital.*, **85**, 659 (1955).

(7) C. A. Benassi, E. Scoffone, G. Galiazzo, and G. Jori, *Photochem. Photobiol.*, **6**, 857 (1967).

(8) Prolonged irradiation of *N*-acetyltryptophan or of *N*-benzyloxycarbonyltryptophan under the same conditions gave no trace of β-carboline derivatives.

TABLE II

FORMATION OF β-CARBOLINES UPON IRRADIATION OF TRYPTOPHAN IN DIFFERENT SOLVENTS[a]

Solvent	Products formed	Yield, %
Acetic acid	1-Methyl-3-carboxy-β-carboline	71
	1-Methyl-β-carboline	24
Propionic acid	1-Ethyl-3-carboxy-β-carboline	70
	1-Ethyl-β-carboline	22
Isobutyric acid	1-Isopropyl-3-carboxy-β-carboline	75
	1-Isopropyl-β-carboline	23
Pivalic acid	1-*tert*-Butyl-3-carboxy-β-carboline	78
	1-*tert*-Butyl-β-carboline	12

[a] The irradiations were carried out in deaerated solution. All other conditions were the same as described in Table I.

In addition, small amounts of the decarboxylated compounds were constantly obtained. In all cases, the formation of decarboxylated products was avoided when tryptophan ethyl ester was the starting material. This allowed us to isolate the corresponding 1-alkyl-β-carbolines in almost quantitative yields.

The rate of conversion of **1a** to β-carbolines increased as the carbon atom adjacent to the carboxyl function of the organic acid changed from primary to secondary and to tertiary (Figure 1). Conversely, no photoreaction of **1a** occurred when the irradiations were run in formic acid or in trichloroacetic acid solution. It thus appears that the presence of electron-donating substituents near the COOH group in the solvent molecule favors the photocyclization process, whereas the reaction is inhibited by the presence of electron-withdrawing groups.

The Reaction Mechanism. A. The Attacking Species.—The stoichiometry of β-carboline formation, as well as the accelerating power of electron-donating groups in the solvent molecule, can be reasonably interpreted by hypothesizing that the organic acid attacks the indole derivatives either as an acylium cation, $R-\overset{+}{C}=O$, or as an acyl radical, $R-\dot{C}=O$. The ability of acetyl radicals to promote the conversion of **1a** to β-carbolines is demonstrated by the following experiment.

Paper chromatographic analysis of 2 m*M* solutions of **1a** in 25% aqueous acetone, which had been irradiated with 254-mμ light (Mineralight lamp), in a N_2 atmosphere, showed that, besides other unidentified products, appreciable amounts of **2a** were produced. Since, under our conditions, almost all of the incident light was absorbed by acetone, it appears reasonable to infer that **2a** is formed by attack from the acetyl radicals deriving from the photolysis of acetone.[9] Furthermore, the presence of radical intermediates in the methylene blue sensitized process can be deduced by the inhibitory effect displayed by radical scavengers, such as hydroquinone.[10]

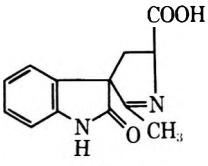
The photoreaction was also inhibited by skatole (3-methylindole). After 1 hr irradiation of an equimolar mixture of skatole and **1a** in deaerated acetic acid, the yield of β-carboline dropped from about 70%

(9) M. I. Christie, J. M. Collins, and M. A. Voisey, *Trans. Faraday Soc.*, **61**, 462 (1965).

(10) In the presence of 10 m*M* hydroquinone, prolonged irradiation caused no detectable modification of tryptophan.

to 22%. Irradiation of skatole alone under the same conditions gave an over 70% yield of 2-acetyl skatole. These findings strongly support the hypothesis that the attacking species is the R–Ċ=O radical, which should originate by an interaction between the photoexcited sensitizer[11] and acetic acid. The detailed features of such interaction are not yet fully understood. A possible reaction pathway involves the photolytic detachment of one $\cdot N(CH_3)_2$ radical from methylene blue and the subsequent attack of the dye radical on acetic acid, leading to the R–Ċ=O species and 3(or 6)-dimethylamino-6(or 3)-hydroxyphenthiazine. Indeed, prolonged irradiation of methylene blue alone in deaerated acetic acid solution led to a major product, whose elemental analysis corresponded to a derivative of methylene blue in which one $N(CH_3)_2$ group has been replaced by an OH group. Moreover, the infrared spectrum of the compound clearly showed the presence of the OH function. The presence of deaminated species among the products of the photobleaching of methylene blue was postulated by Obata.[12]

B. The Position of Attack on Tryptophan.—Charge density calculations[13] indicate that the 2 and 3 positions of the indole ring are the most suitable for an electrophilic attack. The experimental evidence supports this conclusion.[14-16] In our case, it is likely that the radical attack occurs in the 2 position. Actually, 2-hydroxytryptophan failed to undergo any reaction when irradiated under the same conditions as used for tryptophan. If the 3 position had been the site of attack by R–Ċ=O, the spirocycloindolenine **3** should



3

be formed, analogously to what has been observed by other authors[17] for tryptophan derivatives masked in the 2 position. Further evidence supporting our hypothesis is provided by the unique formation of 2-acetylskatole upon methylene blue sensitized irradiation of skatole in deaerated acetic acid solution. On the other hand, the possibility of formation of *N*-acetyltryptophan as an intermediate is ruled out by the failure of this compound to undergo photocyclization to β-carbolines.[8]

A definite demonstration of the intermediate formation of 2-acetyltryptophan was achieved by irradiation of 1 m*M* *N*-*tert*-butoxycarbonyl-L-tryptophan ethyl ester in 80% acetic acid solution, where this compound is quite stable in the dark. After 3 hr of irradiation a photoproduct was isolated which gave a negative response to a colorimetric test with the Ehrlich reagent, showing that the 2 position was masked; its elemental analysis and ir spectrum were consistent with the presence of a $COCH_3$ group. After removal of the *tert*-butoxycarbonyl group by treatment with HCl, the expected **2c** was isolated.

Having established the initial formation of 2-acetyltryptophan, the subsequent step must be the formation of a dihydro-β-carboline by a dark condensation between the side chain NH_2 group and the acetyl group.

C. The Dehydrogenation of the Dihydro-β-carbolines.—Methylene blue can photosensitize the dehydrogenation of the intermediate dihydro-β-carbolines. Actually, we found that, upon irradiation of the dihydro derivative either in acetic acid or in aqueous solution, **2a** is formed with a concomitant enhancement of the photobleaching of methylene blue, which is probably converted to the leuco dye;[18] in particular, after 3 hr of irradiation in deaerated aqueous solution, the presence of 1 m*M* dihydro-β-carboline increased the amount of photobleached dye from 5.7 to about 23%, as deduced from absorbance measurements at 665 mμ. On the other hand, even after prolonged irradiation in the presence of O_2, practically no decoloration of methylene blue was observed. This is in agreement with the well known reversibility of the conversion of this dye to the leuco form.[18]

It is noteworthy that the photodehydrogenation of the dihydro intermediates was efficiently sensitized also by the aforesaid hydroxy derivative of methylene blue. This process may become important in the later stages of the photoreaction.

Experimental Section

All melting points were determined with Kofler micro hot stage and are uncorrected. Spectra were measured with a Cary Model 15 spectrophotometer and with a Perkin-Elmer 317 grating infrared spectrophotometer.

Thin layer chromatography was performed on silica gel coated plates (ascending technique) using the mixture 1-butanol–water–acetic acid (80:20:20, v/v/v) as eluent; paper chromatograms were run on Whatman No. 1 paper (descending technique), using 5% ammonia (solvent 1) and the Partridge mixture (solvent 2) as eluents.

The time course of tryptophan photodegradation was followed by the spectrophotometric procedure detailed elsewhere.[19] The indole derivatives were obtained from Fluka and appeared to be homogeneous by tlc in different solvents. Methylene blue was purchased from Merck; the organic acids were products of Carlo Erba and were distilled under reduced pressure before use. 2-Hydroxytryptophan was kindly supplied by Dr. A. Fontana of this Institute.

Analytical Scale Irradiations.—In all cases, 4 ml of a 1 m*M* substrate solution, added in the dark with an equimolar amount of sensitizer, was introduced into Pyrex test tubes (1.2 × 12 cm) and exposed to the light of four 300-W tungsten lamps, using the same experimental conditions as previously described.[19] The temperature was maintained at 20 ± 1° by circulating water. The solutions were deaerated by bubbling ultrapure N_2 for at least 15 min prior to and during illumination. In some experiments, the irradiations were performed in the presence of hydroquinone or ferrous sulfate in tenfold molar excess over the substrate.

Photocyclodehydrogenation of 3-Substituted Indoles in Acetic Acid.—In a 300-ml Pyrex cylinder was placed 0.5 mmol of substrate, plus an equimolar amount of methylene blue and 250 ml of acetic acid. The vessel was placed in a water bath at 20 ± 1° and irradiated by means of the lamp system described above, at a

(11) The conversion of tryptophan to β-carbolines is completely inhibited by running the irradiation in the presence of Fe^{2+} ions. Since paramagnetic species are known to quench the excited triplet states by enhancing the spin–orbit coupling, this fact suggests that the triplet state of the dye is the reactive intermediate.

(12) H. Obata, *Bull. Chem. Soc. Jap.*, **34**, 1057 (1961).

(13) W. E. Kurtin and P. S. Song, *Photochem. Photobiol.*, **7**, 263 (1968).

(14) A. H. Jackson and P. Smith, *Tetrahedron*, **24**, 2227 (1968).

(15) A. H. Jackson, B. Naidoo, and P. Smith, *Tetrahedron*, **24**, 6119 (1968).

(16) E. Scoffone, A. Fontana, and R. Rocchi, *Biochemistry*, **7**, 971 (1968).

(17) A. H. Jackson and P. Smith, *Tetrahedron*, **24**, 403 (1968).

(18) Y. Usui, H. Obata, and M. Koizumi, *Bull. Chem. Soc. Jap.*, **34**, 1049 (1961).

(19) G. Jori, G. Galiazzo, A. Marzotto, and E. Scoffone, *Biochim. Biophys. Acta*, **154**, 1 (1968).

distance of 40 cm. Deaeration of the solutions was achieved by thoroughly flushing ultrapure N_2 through three porous disks at the bottom of the vessel. When tlc showed total disappearance of the original compound, the irradiation was stopped, the solvent was removed by lyophilization, and the residue was taken up with water and loaded on a column (1.3 × 50 cm) of a carboxylic resin (Amberlite CG-50, 200–400 mesh). The column was eluted with 2% ammonia; 2-ml fractions were collected, which were analyzed by tlc or paper chromatography. In the case of the solutions irradiated in the presence of oxygen, prior to loading on the column, a trace of insoluble material was removed by centrifugation; the residual solution was further purified by preparative paper chromatography,[20] using 5% ammonia as eluent. The blue fluorescent strip was eluted with absolute methanol and taken to dryness.

In the case of tryptamine, one fraction was obtained from the column (R_{f_1} 0.11, R_{f_2} 0.32); crystallization from 80% methanol gave white needles of 1-methyl-β-carboline (**2b**), 64.5 mg (75%) for solutions irradiated in O_2, 80 mg (93%) after irradiations in N_2. The identification of the product was achieved by mixture melting point and by uv and ir comparison with a sample of **2b** prepared independently.[1]

Anal. Calcd for $C_{12}H_{10}N_2$: C, 79.09; H, 5.48; N, 15.68. Found: C, 79.12; H, 5.50; N, 15.62.

In the case of tryptophan ethyl ester, one fraction was again isolated (R_{f_1} 0.18, R_{f_2} 0.42), which was found, after crystallization from absolute methanol, to be 1-methyl-3-ethoxycarbonyl-β-carboline (**2c**) (95.2 mg, 75% after irradiation in O_2; 110.7 mg, 95% after irradiations under N_2): mp 248–249°; uv max (95% methanol) 234 mμ (log ε 4.581), 268.5 (4.202), 334.5 (3.598), 347 (3.605); ir (KBr) 1720 (aryl ester C=O), 1250 and 1120 cm^{-1} (aryl ester CO).

Saponification of **2c** by the method of Tschesche, *et al.*,[21] yielded the free acid (**2a**, yield 85%), identified by mixture melting point and by uv and ir comparison with a sample of authentic **2a**.

Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.81; H, 5.83; N, 5.52. Found: C, 71.02; H, 5.97; N, 5.42.

In the case of tryptophanol, the isolated product (R_{f_1} 0.14, R_{f_2} 0.59) was identified as 1-methyl-3-hydroxymethyl-β-carboline (**2d**): 73.2 mg, 69% after irradiation in O_2; 88.3 mg, 87% after irradiation under N_2; mp 263–265°; uv max (95% methanol) 212 mμ (log ε 4.537), 236 (4.477), 277.5 (4.316), 329 (3.617), 345 (3.588); ir (KBr) 3360 (broad, OH) 1050 cm^{-1} (broad, primary OH).

Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.49; H, 5.66; N, 13.42. Found: C, 73.22; H, 5.78; N, 13.36.

In the case of tryptophanamide, the isolated product (R_{f_1} 0.36, R_{f_2} 0.44) was found to be 1-methyl-3-carbamoyl-β-carboline (**2e**) after crystallization from 80% methanol: 73.1 mg, 65% after irradiation in O_2; 99 mg, 88% after irradiation under N_2; mp 235–237°; uv max (95% methanol) 228 mμ (log ε 4.762), 260.5 (4.573), 288 (4.105), 321 (3.276), 353 (3.421); ir (KBr) 3330 and 3190 (medium, NH), 1645 (amide I), 1630 cm^{-1} (amide II).

Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.35; H, 4.88; N, 18.67. Found: C, 69.48; H, 4.65; N, 18.72.

Photochemical Conversion of Tryptophan to 1-Alkyl-3-carboxy-β-carbolines.—In a typical experiment, 51 mg (0.25 mmol) of tryptophan was dissolved in 250 ml of the appropriate solvent and mixed with an equimolar amount of methylene blue. The solutions were deaerated and irradiated by the experimental arrangement previously described. When all the tryptophan had reacted, as shown by tlc, the irradiation was stopped and the solvent was removed by rotary evaporation and by repeated lyophilization. The residue was taken up with the minimal amount of water and loaded on a column of Amberlite CG-50 (0.9 × 55 cm).

In the case of irradiation in acetic acid solution, elution of the column with water gave one product (40.7 mg, yield 71%), which was identified as 1-methyl-3-carboxy-β-carboline on the basis of elemental analysis and chromatographic R_f values[1] as well as by mixture melting point and uv and ir comparison with a sample of the same product previously prepared.[1] Subsequent elution from the column with 3% ammonia gave a second fraction (10.9 mg, yield 24%), which appeared by elemental, chromatographic, and spectroscopic analysis to be identical with a sample of authentic 1-methyl-β-carboline.[1]

After irradiation in propionic acid solution, elution from the column with water gave one fraction which, after crystallization from 80% methanol, was identified as 1-ethyl-3-carboxy-β-carboline: 47 mg, 70%; mp 295–297°. The melting point, as well as the uv and ir spectra, were coincident with those of a sample of the same product prepared from tryptophan according to Tschesche, *et al.*[2,21]

Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 70.20; H, 5.03; N, 11.59. Found: C, 69.70; H, 5.10; N, 11.55.

Subsequent elution with 3% ammonia gave a second fraction, which was crystallized from methanol and identified as 1-ethyl-β-carboline: 10.8 mg, 22%; mp 244–246°; the uv and ir spectrum were coincident with a sample of the same product prepared from tryptamine by a chemical procedure.[2]

Anal. Calcd for $C_{13}H_{12}N_2$: C, 78.6; H, 6.18; N, 13.98. Found: C, 78.9; H, 6.15; N, 14.15.

After irradiation of tryptophan in the presence of isobutyrric acid as the solvent, elution from Amberlite with water gave one product (R_{f_1} 0.73, R_{f_2} 0.50) which, after crystallization from 80% methanol, was identified as 1-isopropyl-3-carboxy-β-carboline: 47.5 mg, 75%; mp 277–278°; uv max (95% methanol) 232 mμ (log ε 4.603), 279 (4.326), 331 (3.602), 345 (3.613); ir (KBr) 1685 (aryl C=O), 1385 and 1370 cm^{-1} (strong, isopropyl C–H bending).

Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.82; H, 5.55; N, 11.02. Found: C, 70.23; H, 5.62; N, 11.20.

A second fraction (R_{f_1} 0.33, R_{f_2} 0.38) was isolated by elution with 3% ammonia. Crystallization with 80% methanol gave pale yellow needles of 1-isopropyl-β-carboline: 12.6 mg, 23%; mp 225–228°; uv max (95% methanol) 212 mμ (log ε 4.803), 268 (3.992), 307 (2.654), 360 (2.812); ir (KBr) 3345 (indole NH), 1380 and 1370 cm^{-1} (isopropyl C–H bending).

Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.95; H, 6.71; N, 13.33. Found: C, 79.73; H, 6.70; N, 13.42.

Finally, after irradiation in pivalic acid solution, one fraction (R_{f_1} 0.78, R_{f_2} 0.57) was isolated by elution with water; it was crystallized from 80% methanol and identified as 1-*tert*-butyl-carboxy-β-carboline: 52.3 mg, 78%; mp 293–295°; uv max (methanol) 227 mμ (log ε 4.715), 282 (4.22), 332 (3.487), 348 (3.608); ir (KBr) 1685 (aryl C=O), 1390 and 1365 cm^{-1} (weak, *tert*-butyl C–H bending).

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.68; H, 6.34; N, 10.45. Found: C, 71.35; H, 6.35; N, 10.62.

Elution with 3% ammonia yielded a second product (R_{f_1} 0.18, R_{f_2} 0.25), which after crystallization from 80% methanol was shown to be 1-*tert*-butyl-β-carboline: 6.7 mg, 12%; mp 208–211°; uv max (methanol) 208 mμ (log ε 4.77), 271.5 (4.082), 310 (2.835), 353 (2.874); ir (KBr) 3350 (indole NH), 1385 and 1360 cm^{-1} (*tert*-butyl C–H bending).

Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.04; H, 7.14; N, 12.5. Found: C, 79.95; H, 7.08; N, 12.35.

Irradiation of *tert*-Butoxycarbonyl-L-tryptophan Ethyl Ester in 80% Acetic Acid Solution.—The apparatus described above was used to irradiate, under N_2, 20 mg of *tert*-butoxycarbonyl-L-tryptophan ethyl ester and 25 mg of methylene blue dissolved in 40 ml of 80% acetic acid. After 5 hr of illumination, the solvent was removed by lyophilization. Chromatography of the residue on a column of Amberlite CG-50 (see above) yielded 18 mg of one product, which gave a negative color test with the Ehrlich reagent,[5] showing that the 2 position of the indole ring was masked. The ir spectrum (Nujol) showed, besides the peak at 1730 cm^{-1} (aliphatic ester C=O), the presence of a band at 1680 cm^{-1}, which can be assigned to a ketonic –C=O conjugated with an aromatic system. The elemental analysis of the product was in agreement with the expected one for 2-acetyl-*tert*-butoxycarbonyl-L-tryptophan ethyl ester.

Anal. Calcd for $C_{20}H_{26}N_2O_5$: C, 64.17; H, 6.95; N, 7.48. Found: C, 63.98; H, 6.80; N, 7.51.

Removal of the *tert*-butoxycarbonyl group by treating the product (10 mg) with 2 *N* HCl for 3 hr at 50° yielded a new product, whose chromatographic and spectral features were coincident with those found for 1-methyl-3-ethoxycarbonyl-β-carboline (**2c**)

Irradiation of Skatole in Acetic Acid Solution.—The apparatus described above was used to irradiate, under N_2, 20.8 mg of skatole and 32 mg of methylene blue dissolved in 40 ml of acetic acid. After 3 hr of illumination, tlc showed that skatole (R_{f_2} 0.95) was almost completely converted to one product (R_{f_2} 0.83), which

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(21) R. Tschesche, H. Jenssen, and P. M. Rangachari, *Chem. Ber.*, **91**, 1732 (1958).

gave negative color tests with the Ehrlich reagent,[5] suggesting that the 2 position of the indole moiety was masked. The product was isolated by chromatographing the lyophilized residue on a column (1.0 × 42 cm) of the sulfonic resin Dowex-50, using 1% ammonia as eluent: 21.2 mg, 72.7%; the ir spectrum (KBr) gave a peak at 1690 cm^{-1}, clearly showing the presence of a carbonyl group conjugated with an aromatic system; the elemental analysis was in agreement with the expected one for 2-acetylskatole.

Anal. Calcd for $C_{11}H_{11}NO$: C, 74.68; H, 6.79; N, 8.64. Found: C, 74.19; H, 6.85; N, 8.65.

Irradiation of Methylene Blue in Acetic Acid Solution.—In one experiment, 100 mg of methylene blue in 250 ml of acetic acid were irradiated for 40 hr under N_2 by the apparatus previously described. Tlc analysis showed that methylene blue was slowly converted to three products. The major product (R_{f_2} 0.65) was isolated by chromatographing the lyophilized irradiated mixture on an alumina column (2 × 50 cm), using a 1:1 (v/v) CH_3OH–$CHCl_3$ mixture as eluent. The visible absorption maximum of the product in chloroform was located at 625 mμ; such a blue shift with respect to methylene blue (absorption maximum 637 mμ) was observed by Obata[12] for hydroxyphenthiazines. The ir spectrum (KBr) differed from that of methylene blue for the presence of a broadened band at 3340 cm^{-1} and of a doublet at 1200 cm^{-1}, as it is typical of phenolic OH. On the basis of these evidences, we tentatively identify the product as 3(or 6)-hydroxy-6(or 3)-dimethylaminophenothiazine.

Anal. Calcd for $C_{14}H_{14}N_2SO$: C, 61.84; H, 5.58; N, 12.02; S, 13.75. Found: C, 61.73; H, 5.55; N, 12.10; S, 13.69.

Registry No.—**2a**, 22329-38-0; **2b**, 486-84-0; **2c**, 33821-71-5; **2d**, 33821-72-6; **2e**, 23256-12-4; tryptophan, 6159-33-7; 1-ethyl-3-carboxy-β-carboline, 33821-74-8; 1-ethyl-β-carboline, 20127-61-1; 1-isopropyl-3-carboxy-β-carboline, 33821-76-0; 1-isopropyl-β-carboline, 22314-95-0; 1-*tert*-butyl-3-carboxy-β-carboline, 33821-78-2; 1-*tert*-butyl-β-carboline, 33821-79-3; 2-acetyl-*tert*-butoxycarbonyl-L-tryptophan ethyl ester, 33821-80-6; 2-acetylskatole, 16244-23-8; methylene blue, 61-73-4; 3-hydroxy-6-dimethylaminophenthiazine, 33821-82-8; 6-hydroxy-3-dimethylaminophenthiazine, 33821-83-9.

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Mechanism and Catalysis for Furfural Phenylhydrazone Formation[1]

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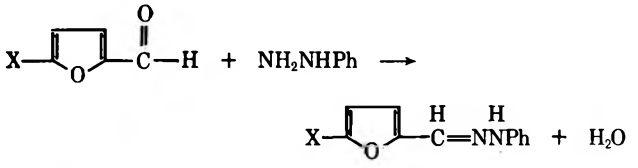
As is typical for the addition of amines to carbonyl compounds, the reaction of 5-substituted furfurals with phenylhydrazine exhibits rate-determining attack of the nucleophile under acidic conditions and rate-determining decomposition of the carbinolamine intermediate under neutral and basic conditions. The attack of phenylhydrazine on these substrates is subject to general acid catalysis by carboxylic acids, the Brønsted exponent $\alpha = 0.35$. Dehydration of the carbinolamine intermediates occurs *via* acid-catalyzed, pH-independent, and, in the case of the nitro derivative, base-catalyzed reaction pathways.

The principal features of the mechanisms for addition of weakly basic amines to carbonyl compounds[2,3] have been derived from a series of studies employing simple aliphatic and aromatic aldehydes and ketones.[4-12] Both to broaden the basis upon which our conclusions are founded and to explore substituent effects in heterocyclic aromatic systems, the kinetics of 5-substituted furfural phenylhydrazone formation have been investigated. While this study has, for the most part, reinforced previous conclusions, some interesting differences in detail do appear. The results are presented below.



Experimental Section

Materials.—5-Methylfurfural was prepared according to the method of Rinkes,[13] bp 84–86° (3 mm) [lit.[13] bp 83–85° (15 mm)]. The product is stable for several months at −10° in the absence of light and oxygen. Dilute solutions in 20% aqueous ethanol were found to be stable for several days at 0° in the dark. 5-Bromofurfural, mp 84° (lit.[14] mp 82°), and 5-nitrofurfural, mp 35–36° (lit.[15] mp 35–36°), were also prepared according to published procedures.[14-16] All other reagents employed were obtained commercially and, with the exception of reagent grade inorganic salts, were either redistilled or recrystallized prior to use. Solutions of phenylhydrazine were prepared just prior to use, as were those of carboxylic acids in 20% ethanol, to avoid formation of the ethyl esters.

Kinetic measurements[4,6,9] were carried out spectrophotometrically at 25° with the aid of a Zeiss PMQ II spectrophotometer equipped with a cell holder through which water from a thermostated bath was continuously circulated. Reaction kinetics were monitored by observing the appearance of the furfural phenylhydrazones at appropriate wavelengths in solutions containing initial concentrations of the aldehydes of 5×10^{-5} *M:* 5-methyl, 343 nm; unsubstituted, 340 nm; 5-bromo, 348 nm; 5-nitro, 464 nm. In all cases a sufficient excess of phenylhydrazine was employed to ensure that pseudo-first-order kinetic behavior would be obtained. First-order rate constants were evaluated from plots of log ($OD_\infty - OD_t$) against time in the usual manner. Second-order rate constants were obtained by dividing first-order constants by the concentration of phenylhydrazine free base. In the pH region in which phenylhydrazine attack is principally rate-determining, rate constants have been

(1) Supported in part by the Conselho Nacional de Pesquisas and by the Fundação de Amparo à Pesquisa do Estado de São Paulo.

(2) W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964).

(3) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969.

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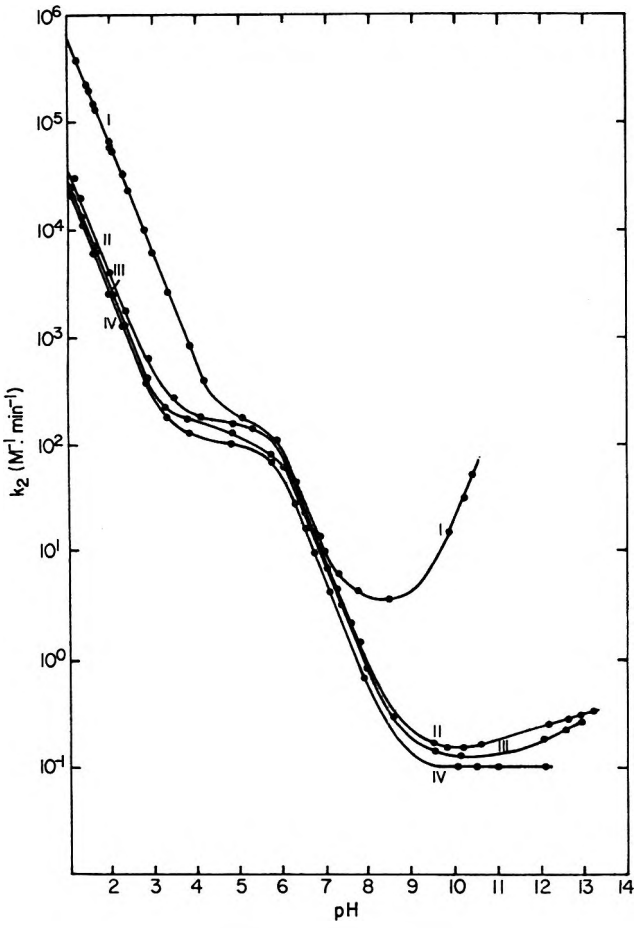

Figure 1.—Logarithms of second-order rate constants for phenylhydrazone formation from a series of 5-substituted furfurals in 20% ethanol at 25° and ionic strength 0.50 plotted as a function of pH. All points refer to zero buffer concentration. I, 5-nitrofurfural; II, 5-bromofurfural; III, furfural; IV, 5-methylfurfural.

corrected to account for the influence of the rate of carbinolamine dehydration as described by Sayer and Jencks.[10] Catalytic (third-order) rate constants were evaluated from the slopes of plots of second-order constants against the concentration of catalyst. All kinetic experiments were carried out in 20% ethanol at an ionic strength of 0.50, maintained with KCl, with 2×10^{-4} *M* EDTA. Values of apparent pH were recorded with a Radiometer Model PHM 4d pH meter equipped with a glass electrode. Calculations of the concentration of phenylhydrazine free base and undissociated carboxylic acids were made employing the Henderson–Hasselbalch equation and values of pK_a which refer to a solvent of water at zero ionic strength. Because of the opposing effects of high ionic strength and organic solvent on the values of pK_a, use of the indicated values is not unreasonable.[9] At any event, there is no conclusion drawn below that would be significantly modified by the choice of slightly different values of pK_a.

Product Analysis.—The products of condensation of phenylhydrazine with furfural, 5-methylfurfural, and 5-nitrofurfural were identified as the corresponding phenylhydrazones from their characteristic ultraviolet and infrared spectra. 5-Bromofurfural phenylhydrazone was prepared by mixing a solution of 1.0 g of phenylhydrazine hydrochloride in water with 50 ml of an ethanol solution containing 1.0 g of 5-bromofurfural. Yellow crystals of the phenylhydrazone, which became dark green upon drying, were obtained by the addition of small amounts of water after cooling the solution to 0°, mp 68–70°. *Anal.* Calcd: C, 49.83; H, 3.04. Found: C, 50.18; H, 3.17. The phenylhydrazone exhibited an absorption maximum at 358 nm.

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Results and Discussion

Subsequent to the formulation of the Hammett equation,[17] a very large amount of experimental information concerning the effects of polar substituents on reaction rates and equilibria has been correlated with the appropriate substituent constants in the benzene series.[18–21] The only other aromatic nucleus treated in any detail is that of naphthalene.[22] Treatment of heterocyclic aromatic systems is quite limited, although some preliminary efforts have been made.[19,21,23] A set of σ_F[2,5] substituent constants (the designation of these constants follows the form employed by Dewar for the naphthalene system[22]) for 5-substituted 2-furyl derivatives has been calculated from the dissociation constants in water of the corresponding furoic acids.[24] These are linearly related to the usual σ constants, $\sigma_F^{2,5} = 1.40\sigma_p$. This result suggests that, for dissociation of the acids at least, the relative importance of inductive and resonance effects of polar substituents in the two cases is similar. Extension of this concept to nucleophilic reactions of the corresponding aldehydes is, as is developed below, not straightforward.

In Figure 1, second-order rate constants, extrapolated to zero buffer concentration where necessary, for phenylhydrazone formation from 5-substituted furfurals are plotted as a function of pH. The general shape of the curves is familiar and reflects (going from acidic to basic conditions) acid-catalyzed and water-catalyzed attack of the nucleophile, pK_a 5.2, as the rate-determining step and acid-catalyzed, water-catalyzed, and base-catalyzed dehydration of the carbinolamine intermediate as the rate-determining step.[2–4,9]

In the region of rate-determining attack of phenylhydrazine, the second-order rate constants are sensitive functions of the nature and concentration of buffers employed to maintain constant pH. Studies of the buffer catalysis demonstrated that, as usual, the catalysis is of the general acid type. As noted by Sayer and Jencks,[10] estimation of catalytic constants for the carboxylic acids for reactions of this type can be complicated by the varying importance of the rate of carbinolamine dehydration to the overall rate as a function of pH and buffer concentration. To avoid this difficulty, all second-order rate constants have been corrected to account for the influence of the rate of carbinolamine dehydration. Catalytic constants for various carboxylic acids were then evaluated in the usual way. These constants are collected in Table I. As may be judged from Figure 1, the rates for carbinolamine formation and dehydration are much more nearly equal for 5-nitrofurfural than for other substrates. One consequence of this fact is that, for this substrate, plots of uncorrected second-order rate constants against

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TABLE I

CATALYTIC CONSTANTS OF SEVERAL ACIDS, EXPRESSED IN M^{-2} min^{-1}, FOR THE ATTACK OF PHENYLHYDRAZINE ON A SERIES OF 5-SUBSTITUTED FURFURALS IN 20% ETHANOL, AT 25° AND IONIC STRENGTH 0.50

Catalyst	pK_a	5-Methylfurfural	Furfural	5-Bromofurfural	5-Nitrofurfural
H_3O^+	−1.74	2.8×10^5	3.3×10^5	4.0×10^5	6.0×10^6
$NCCH_2CO_2H$	2.45		2.6×10^4		7.9×10^5
$ClCH_2CO_2H$	2.90	1.2×10^4	1.6×10^4	2.6×10^4	4.8×10^5
HCO_2H	3.75		8.3×10^3		3.5×10^5
$BrCH_2CH_2CO_2H$	4.00		9.2×10^3		2.4×10^5
CH_3CO_2H	4.76	4.6×10^3	4.8×10^3	5.0×10^3	4.1×10^4
PHH^+ [a]	5.20	1.3×10^4	2.1×10^4	3.1×10^4	3.2×10^4
H_2O	15.74	3.0	3.3	3.6	4.6

[a] Phenylhydrazinium ion.

catalyst concentration are nonlinear. Related cases identified include benzaldehyde semicarbazone and thiosemicarbazone formation.[6,10] Data of this type can also be the consequence of complexation of carboxylate ions with the aldehyde substrates to form unreactive species; *p*-nitrobenzaldehyde phenylhydrazone formation appears to provide one example of this type.[9]

Catalytic constants for the carboxylic acids are well correlated by the Brønsted catalysis law: least-squares treatment of the data yields a value of α of 0.35 for both furfural and 5-nitrofurfural. The same value of α has been obtained for general acid catalysis of benzaldehyde phenylhydrazone formation,[9] but smaller values appear to characterize a number of related reactions.[10]

Correlation of the rate constants for the attack of phenylhydrazine on the 5-substituted furfurals by the σ_F[2,5] substituent constants or by σ or σ^+ substituent constants fails. Examination of the data in Table I reveals the source of difficulty. With weakly acidic catalysts, including water, acetic acid, and phenylhydrazinium ion, the rate constants are quite insensitive to the nature of the polar substituent (and can, therefore, be correlated by essentially any set of substituent constants) while for more acidic catalysts, the 5-nitrofurfural is markedly more reactive than the other three substrates whose rate constants are, as above, rather insensitive to the nature of the polar substituent. While the reasons for the distinctive behavior of the 5-nitro derivative are not clear, it does suggest that, just as in the benzene series, a special set of substituent constants may be necessary to correlate rate constants for reactions involving electrophilic species in the furan series.

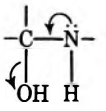
The rate constants for the water-catalyzed attack reaction are less sensitive to the nature of the polar substituent than are those for the acid-catalyzed reaction (Figure 1 and Table I). This situation is quite the opposite of that usually observed[6,9] for reactions of this class and is difficult to rationalize on the basis of the mechanism usually written for these reactions.[2,3,6] It is possible that this observation reflects the importance of the heterocyclic oxygen of the furan ring as a participant in the reaction through hydrogen bond formation with the catalyst *via* intervening water molecules. It is clear that a full explanation will await more detailed understanding of substituent effects in this system.

Rate constants characterizing the various reaction pathways for furfural phenylhydrazone formation under conditions of rate-limiting dehydration are collected in Table II. The acid-catalyzed pathway is quite insensitive to the nature of polar substituents; similar observations have been made for related reactions.[6,9,25] In contrast, the rate constants for the water-catalyzed (or uncatalyzed) reactions increase substantially with increasing electron withdrawal in the polar substituent (the rate constant for the 5-nitro derivative was evaluated by subtracting the rate constant for the acid-catalyzed and base-catalyzed reactions at the rate minimum). This reaction must occur in the following way (the corresponding reaction for Schiff base hydrolysis is known to occur with attack of hydroxide ion on the protonated substrate).[26,27]

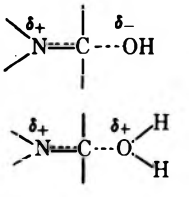
TABLE II

RATE CONSTANTS FOR THE ACID-CATALYZED, pH-INDEPENDENT, AND BASE-CATALYZED REACTIONS FOR 5-SUBSTITUTED FURFURAL PHENYLHYDRAZONE FORMATION UNDER CONDITIONS OF RATE-DETERMINING CARBINOLAMINE DEHYDRATION

Substituent	$k_H \times 10^{-7}$, M^{-2} min^{-1}	k_{H_2O}, M^{-1} min^{-1}	k_{OH}, M^{-2} min^{-1}
Nitro	9.0	2.5	2.0×10^5
Bromo	8.0	0.31	
Unsubstituted	8.0	0.20	
Methyl	5.0	0.10	



The fact that the acid-catalyzed dehydration of the carbinolamine is less sensitive to the nature of polar substituents than is the uncatalyzed process suggests that the transition states for the two reactions may differ significantly in the extent of carbon–oxygen bond cleavage.



With the good leaving group, water, little C–O bond cleavage in the transition state is visualized, minimizing the effects of polar substituents. With the poorer leaving group, hydroxide ion, it is reasonable to assume

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a greater degree of progress toward sp^2 geometry at the transition state, increasing the extent of interaction, particularly by resonance, between the reaction center and polar substituents.

Dehydration of the carbinolamine derived from 5-nitrofurfural and phenylhydrazine is markedly susceptible to base catalysis, while those derived from other furfurals exhibit very small contributions from this pathway. Thus the polar effects on the base-catalyzed pathway are the largest for this particular dehydration pathway as they are for dehydration of benzaldehyde phenylhydrazine carbinolamine.[4] As above, this behavior must reflect the importance of electron withdrawal in the formation of the double bond in the product.

Registry No.—Phenylhydrazone, 100-63-0; 5-bromofurfural phenylhydrazone, 34220-06-9; 5-methylfurfural, 620-02-0; furfural, 98-01-1; 5-bromofurfural, 1899-24-7; 5-nitrofurfural, 698-63-5.

Acknowledgment.—The author is indebted to Dr. Eugene H. Cordes for helpful comments concerning this work.

The Influence of Configuration on Transmission of Electronic Effects in α,β-Unsaturated Ketones

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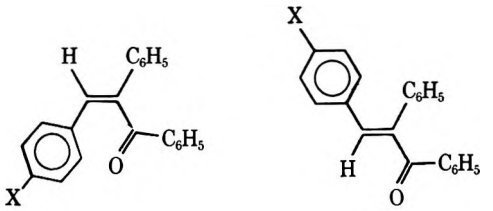
A series of zusamen (Z)- and entgegen (E)-α-phenylchalcones (1,2-diphenyl-3-arylpropenones) have been prepared and configurational assignments have been made to them. Their carbonyl stretching frequencies have been measured in carbon tetrachloride solutions. A good linear free-energy relationship was obtained between ν(C=O) and σ^+ for the E isomers (r = 0.980). On the other hand, the Z isomers gave only a poor correlation (r = 0.798). An unprecedentedly large ρ_E/ρ_Z ratio of ~6 was observed. The ρ value for the Z isomers suggests that this system is essentially insensitive to substituent effects. The data were also treated using the Swain–Lupton approach. Comparisons of the linear free-energy results obtained from the α-phenylchalcone system are made with other analogous systems.

The alteration of transmission of electronic effects through an intervening link by changing the geometric relationship between substituent and reaction site has been noted in several systems.[2] In aliphatic systems a change from E to Z isomers resulted in an increase in sensitivity to substituents as judged by the magnitudes of the Hammett ρ values and this observation has been attributed to field effects. In aryl systems a reduction in sensitivity to substituents with the same configurational change has been noted. In spite of growing interest and an increasing number of reports on linear free-energy relationships of α,β-unsaturated ketone systems,[3,4] the effect of geometric alterations on substituent effect transmission in such systems does not appear to have been reported. To attempt to assess this effect and as a continuation of a general investigation[4] of linear free-energy relationships of α,β-unsaturated ketones, we have measured the carbonyl stretching frequencies [ν(C=O)] of a series of (Z)- and (E)-α-phenylchalcones [1,2-diphenyl-3-(para-substituted phenyl)propenones] (I and II).



I

II

α-Phenylchalcones.—The α-phenylchalcones were prepared using the approach previously described by Stobbe[5] which usually resulted in a mixture of (Z)- and (E)-α-phenylchalcones. Frequently, the reaction sequence gave mainly the E isomer, and consequently to acquire adequate amounts of the Z isomer the E isomer was subjected to photoequilibration type conditions and the resulting mixtures were separated by column chromatography.

The configurations of the isomers were assigned on the basis of the extinction coefficient of their uv absorption maximum in analogy with the assignments made for **5**, **13**, **8**, and **16** by Lutz and Black.[6] The series of compounds assigned the E configuration consistently, with the exception of **16** as previously noted,[6] exhibited absorption maxima at wavelengths longer than the Z isomers. The series assigned the Z configuration exhibited ν(C=O) bands which were at higher frequencies, generally about 10 cm^{-1}, than the corresponding E isomers (see Table I). This is in accord with the idea that the steric interaction of the 3-aryl group with the benzoyl group in the Z isomer results in the deconjugation of the carbonyl and styryl groups and hence a shift of ν(C=O) to higher frequency. The configurational assignments[6] to the parent members of this series made by consideration of uv absorptions have now been independently confirmed by ir measurements.

(1) American Chemical Society Petroleum Research Fund Scholar.

(2) (a) K. Bowden and D. C. Parkin, *Can. J. Chem.*, **46**, 3909 (1968); (b) R. Fuchs and J. J. Bloomfield, *J. Org. Chem.*, **31**, 3423 (1966); (c) M. Charton, *ibid.*, **30**, 974 (1965); (d) A. B. Turner, R. E. Lutz, N. S. McFarlane, and D. W. Boykin, Jr., *ibid.*, **36**, 1107 (1971); (e) J. J. Bloomfield and R. Fuchs, *ibid.*, **26**, 2991 (1961); (f) R. Fuchs, C. A. Kaplan, J. J. Bloomfield, and L. F. Hatch, *ibid.*, **27**, 733 (1962).

(3) (a) J. R. Dimmock, P. L. Carter, and P. D. Ralph, *J. Chem. Soc. B*, 698 (1968); (b) S. Toma and A. Perjessy, *Chem. Zvesti*, **23**, 343 (1969); (c) A. Perjessy, *ibid.*, **23**, 905 (1969).

(4) (a) N. L. Silver and D. W. Boykin, Jr., *J. Org. Chem.*, **35**, 759 (1970); (b) M. L. Ash, F. L. O'Brien, and D. W. Boykin, Jr., *ibid.*, **37**, 106 (1972); (c) W. F. Winecoff, III, and D. W. Boykin, Jr., *ibid.*, **37**, 674 (1972); (d) R. W. Woodard and D. W. Boykin, Jr., *Chem. Commun.*, 628 (1970).

(5) H. Stobbe and F. J. Wilson, *Ann.*, **374**, 237 (1910).

(6) W. B. Black and R. E. Lutz, *J. Amer. Chem. Soc.*, **75**, 5990 (1953).

TABLE I

α-PHENYLCHALCONES

Z isomers			E isomers		
Compd	X	ν(C=O), cm⁻¹	Compd	X	ν(C=O), cm⁻¹
1	p-CH_3O	1670.6	9	p-CH_3O	1657.7
2	p-CH_3	1671.4	10	p-CH_3	1660.1
3	p-C_6H_5	1671.6	11	p-C_6H_5	1660.7
4	p-F	1670.7	12	p-F	1661.5
5	p-H	1671.1	13	p-H	1660.8
6	p-Cl	1672.0	14	p-Cl	1662.6
7	p-Br	1671.6	15	p-Br	1663.2
8	p-NO_2	1672.4	16	p-NO_2	1667.6

Linear Free-Energy Relationships.—The values for ν(C=O) for eight geometric pairs of α-phenylchalcones measured in carbon tetrachloride solution are listed in Table I. The difference in ν(C=O) for the p-methoxy- (**9**) and the p-nitro- (**16**) (*E*)-α-phenylchalcones, ~10 cm^{-1}, provides an ample spread in σ values for developing a significant linear free-energy relationship. On the other hand the analogous difference in the *Z* series is only ~2 cm^{-1}. In view of the error in measurement of ν(C=O) interpretation of correlations derived from the *Z* series should be viewed with some skepticism.

Both configurational isomers show shoulders on the carbonyl band. The shoulders presumably arise from conformational bands. It is assumed that lack of assignment of these bands is of no particular consequence to this study, since it has been shown that effectiveness of transmission does not vary over a range of about 30% for conformational isomers in several other α,β-unsaturated ketone systems.[4c]

The stretching frequencies of both isomeric series have been correlated with σ^+ values taken from reported tabulations.[7] Figure 1 contains a graphical presentation and Table II contains the results of statistical treatment[8] for both series. A good correlation is observed for the *E* series (r = 0.980), whereas a poor correlation is obtained with the *Z* system (r = 0.798).

TABLE II

RESULTS OF STATISTICAL TREATMENT USING σ^+ CONSTANTS[a,b]

System	n	ρ	s	i	c
(*Z*)-Chalcone	8	1.10	0.40	1671.5	0.798
(*E*)-Chalcone	8	6.35	0.62	1662.0	0.980
(*E*)-APCA[c]	7	7.07	2.64	1674.0	0.826

[a] See ref 4a and 8. [b] *n*, number of points; ρ, slope as determined by method of least squares; *s*, standard deviation; c, correlation coefficient; *i*, intercept. [c] Data taken from ref 9; values used for p-CH_3O, p-CH_3, p-H, m-CH_3O, p-Cl, m-Cl, and p-NO_2 substituents. See also footnote 10.

Comparison of the ρ value (6.35) obtained from the *E* series with the value (5.36) obtained from five similarly substituted chalcones[4a] shows that there is little change in the effectiveness of the transmission of electronic effects by the addition of the α-phenyl group to the (*E*)-chalcone system. This suggests that a serious steric effect on the chalcone system is not introduced by the addition of a large group and that the inductive effect of the α-phenyl is not detrimental to transmission. The implication is that the β-phenyl and the benzoyl group remain essentially coplaner. This conclusion is in accord with ones previously drawn from uv studies.[6]

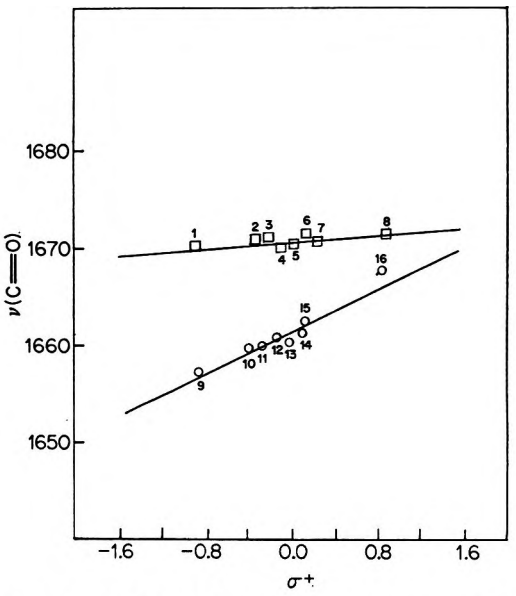


Figure 1.—Plot of ν(C=O) *vs.* σ^+: □, *Z* isomers; ○, *E* isomers.

An investigation of the effect of substituents on the carbonyl stretching frequency of substituted α-phenylcinnamic acids (APCA), measured in the solid state, has been reported.[9,10] Table II contains the results of least-squares treatment of the (*E*)-APCA data. The correlation is poor; nevertheless, the ρ value is approximately that which we note for the (*E*)-α-phenylchalcones.[10]

The ρ value for the (*Z*)-α-phenylchalcone series is dramatically different from the *E* value even bearing in mind the error in measurement for the *Z* series. Essentially, the *Z* series is insensitive to substituent effects. This profound difference between geometric isomers is unprecedented. Previous studies of the effect of geometry on transmission of electronic effects in aryl systems have shown, by comparing ρ_E:ρ_Z ratios, that the *Z* isomers generally transmit electronic effects from ~50% as effectively to equally as well as the corresponding *E* isomers.[2] Table III contains a comparison of ρ_E:ρ_Z for several sets of closely related geometric pairs. The ρ_E:ρ_Z value reported here for the α-phenylchalcones is greater than those shown in the table by a

TABLE III

ρ-VALUE COMPARISON FOR *Z* AND *E* ISOMERS

System	Reaction	ρ_E:ρ_Z	Ref
α-Phenylchalcones	ν(C=O)	5.8	This work
α-Phenylcinnamic acids	Ionization	1.2	2a
α-Phenylcinnamic acids	Esterification	1.9	2a
Cinnamic acids	Ionization	1.4	2e
Cinnamic esters	Saponification	1.1	2e
Phenylbenzoylaziridines	Nmr chemical shifts	1.4	2d
Phenylcyclopropanecarboxylic acids	Ionization	1.1	2f
Phenylcyclopropanecarboxylic esters	Saponification	0.8	2f

(7) C. D. Ritchie and W. F. Sager in "Progress in Physical Organic Chemistry," Vol. 2, Interscience, New York, N. Y., 1964.

(8) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).

(9) C. W. Bird and E. M. Briggs, *Spectrochim. Acta*, **25A**, 899 (1969).

(10) Data for only four *Z* isomers were reported and interestingly the ν(C=O) value for the p-NO_2 compound was at some 5-cm^{-1} lower frequency than that of the p-CH_3O analog. Therefore, we have not treated the reported data for this *Z* series by our statistical approach.

TABLE IV

RESULTS OF STATISTICAL TREATMENT USING F AND R CONSTANTS[a]

System	n	f	r	i	E	C	% R
(Z)-Chalcone	8	0.528 ± 0.346	2.30 ± 0.72	1671.5	0.374	0.858	64 ± 17
(E)-Chalcone	8	4.63 ± 0.430	9.66 ± 0.890	1661.1	0.465	0.991	46 ± 3
(E)-APCA[b]	7	6.56 ± 1.86	9.76 ± 3.15	1673.1	1.80	0.939	46 ± 11
(Z)-APCA[c]	5	−0.423 ± 0.044	−0.526 ± 0.088	5.61	0.041	0.994	35 ± 5
(E)-APCA[c]	5	−0.444 ± 0.122	−0.857 ± 0.244	6.92	0.113	0.974	46 ± 10
(Z)-APCA[d]	5	0.180 ± 0.020	0.191 ± 0.040	0.980	0.019	0.993	32 ± 5
(E)-APCA[d]	5	0.301 ± 0.042	0.494 ± 0.084	0.02	0.039	0.992	42 ± 5

[a] Swain–Lupton field and resonance parameters; see ref 11. These correlations were made using a multiple linear regression program written using the statistical analysis described in ref 11. Calculations were carried out on an IBM 7094 computer. % R values were calculated by the approach used in ref 4a. n, number of points; f, regression coefficient for field parameter; r, regression coefficient for resonance parameter; i, intercept; E, standard error of estimate; C, multiple correlation coefficient; % R defined in ref 4a. [b] The stretching frequency data for α-phenylcinnamic acids in the solid state have been reported.[9] The E isomers used in this correlation were those listed in Table II, footnote c. See also ref 10. [c] Correlation of pK data is reported for α-phenylcinnamic acids in ref 2a. Substituents used were p-H, p-CH_3O, p-CH_3, p-Cl, and p-NO_2. [d] Correlation of rate constants for esterification of α-phenylcinnamic acids with diphenyldiazomethane is reported in ref 2a. The substituents were the ones listed in c above.

factor of at least 3. The large difference may be the result of a greater degree of steric interactions in the more sterically complicated α-phenylchalcones in comparison with other less substituted systems. On the other hand, this difference may reflect the fact that most of the ρ_E:ρ_Z ratios in Table III are derived from reaction data where developing charges make more extensive demands upon the substituents and thereby force a greater degree of coplanarity between the Z groups in question. To test this point, other geometric pairs should be investigated by methods which assess ground-state substituent effects.

Swain and Lupton[11] have developed a method which evaluates the significance of the resonance and field effect contributions to a two parameter linear free-energy relationship. The results of the treatment of the data for the (Z)- and (E)-α-phenylchalcones by this approach are listed in Table IV. Included for comparison with the α-phenylchalcone data in Table IV are the results from treatment of ir and reaction data previously reported on the APCA system.[2a,9,10]

It was noted (*vide supra*) that the Hammett ρ value for II was significantly greater than the value for I. If % R values are a measure of the transmission of resonance effects it can be seen from Table IV that there is no significant effect on transmission by resonance with changes in the geometric relationships of the molecule. The correlation for I is poor and consequently makes this observation tenuous at best for this system. On the other hand, the reactivity data listed in Table IV, for which good correlations are obtained, show little, if any, difference between the contribution of resonance to the correlation for the (Z)- and (E)-α-phenylcinnamic acids. Whether these results should be interpreted as evidence for the invalidity of the Swain–Lupton approach or as evidence which requires the rejection of the idea that diminution of transmission of electronic effects in the Z series is a result of deconjugation of the substituent and the reaction site remains to be tested by an independent approach.

Experimental Section

Infrared Frequencies.—The ir stretching frequencies for all of the α-phenylchalcones were determined using a Beckman IR-12 grating spectrometer in the expanded scale mode at scan rates of 8 cm^{-1} min, chart speeds of 1 in./min, and period setting of 8 (see ref 4a for comments on error). The spectra were taken on ~5% solutions of the compounds in spectral grade carbon tetrachloride at 35 ± 4° in a matched set of KBr cells of path length 0.05 mm. A weak band appeared at 1652 cm^{-1} in the spectra of all of the α-phenylchalcones, both E and Z isomers. The height of each band was measured as the distance from the maximum absorption of the 1652-cm^{-1} band to the point of maximum absorption of the carbonyl band. The frequencies were taken as the point at 25% of the height at half-band width and this value was determined by measurement from said point to a premarked wavenumber. The values shown in Table II are the average of six different scans taken on two separate days all of which gave frequencies which were within 0.3 cm^{-1} of one another. The carbonyl band of 1 was atypically complex; its band width was approximately twice as broad as the other E isomers. The band width used for determining ν(C=O) for 1 was obtained by superimposition of the spectrum of 2 on that of 1 and graphically plotting in the band shape. The ν(C=O) values deduced for 1 by other procedures resulted in values which deviated significantly from the Hammett line.

α-Phenylchalcones.—The approach used to prepare the α-phenylchalcones is similar to that described by Stobbe.[5] Anhydrous HCl was passed through a molten mixture of 0.05 mol of deoxybenzoin and 0.1 mol of substituted benzaldehyde for 4 hr. The resulting solid 3-chloro-3-aryl-1,2-diphenylpropanone was

TABLE V

α-PHENYLCHALCONES[a]

Compd	Mp (lit. mp), °C	λ, nm (ε × 10^{-3})	λ, nm (ε × 10^{-3})
	Z Isomers		
1	113–114 (113)[b]	257 (25.7)	294 (28.8)
2	91–92	260 (24.3)	286 (26.1)
3	163–164.5	260 (20.1)	306 (34.2)
4	115–117.5	259 (23.4)	279 (21.1)
5	85–87 (88–89)[c]	260 (20.3)	282 (19.4)
6	101–102	260 (29.8)	285 (30.6)
7	95–97	261 (26.6)	287 (28.2)
8	167–168 (168–168.5)[c]	251 (21.6)	328 (20.4)
	E Isomers		
9	84–85 (85)[b]	252 (17.4)	315 (18.9)
10	94–94.5	252 (15.4)	312 (16.9)
11	184–186	253 (20.3)	325 (26.3)
12	107–110	254 (16.4)	303 (14.4)
13	99–101 (103–103.5)[c]	250 (17.1)	299 (15.1)
14	98–100	255 (17.0)	304 (16.5)
15	96–98	255 (16.2)	305 (15.9)
16	155–157 (153–153.5)[c]	257 (16.3)	318 (16.4)

[a] All compounds except 5, 8, 13 and 16 were analyzed for C and H and all results were within ±0.3 of theory. [b] These isomers have been previously reported [A. Klages and F. Tetzner, *Ber.*, 35, 3965 (1902)]; however, configurational assignments were not made. [c] Configurational assignments were made in ref 6.

(11) C. G. Swain and E. C. Lupton, Jr., *J. Amer. Chem. Soc.*, **90**, 4328 (1968).

washed with small quantities of cold ethanol followed by small quantities of ether. The crude chloropropanones, usually ~10 g, were used directly without further purification. Crude chloropropanone was dissolved in 250 ml of ethanol containing 0.3 mol of piperidine and refluxed for 24 hr. The solvent was evaporated under reduced pressure and the resulting residue was taken up in ether and washed with 5% HCl and with H_2O, dried ($CaSO_4$), and evaporated. The crude residue was placed on a chromatograph column packed with Al_2O_3. The eluent was typically benzene–low boiling petroleum ether mixtures.[12] The *Z* isomers were the first isomers to be eluted. Frequently, to obtain reasonable quantities of the *Z* isomers, benzene solutions of $\sim 10^{-3}$ *M* *E* isomers were irradiated for 24 hr with a 320-W uv lamp fitted with a 2537-A light source. The product of the irradiation was chromatographed as described above. The physical properties of the α-phenylchalcones prepared in this way are listed in Table V.

Table V contains melting points obtained with a Thomas–Hoover Uni-Melt and they are corrected. Also, Table V contains uv data obtained for the α-phenylchalcones in $\sim 10^{-5}$ *M* absolute ethanol solutions on a Beckman DK-2 spectrometer. Analyses were obtained by Atlantic Microlab, Atlanta, Ga.

(12) *Cf.* L. E. Friedrich and R. A. Cormier, *J. Org. Chem.*, **35**, 450 (1970).

Registry No.—**1**, 34236-57-2; **2**, 34236-58-3; **3**, 34236-59-4; **4**, 34236-60-7; **5**, 7512-67-6; **6**, 34236-62-9; **7**, 34236-63-0; **8**, 34236-64-1; **9**, 34236-65-2; **10**, 34236-66-3; **11**, 34236-67-4; **12**, 34236-68-5; **13**, 7474-65-9; **14**, 34236-70-9; **15**, 34236-71-0; **16**, 34236-72-1.

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Notes

The Rearrangement of 11,11-Dibromotricyclo[4.4.1.0^{1,6}]undecane

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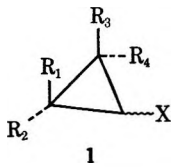
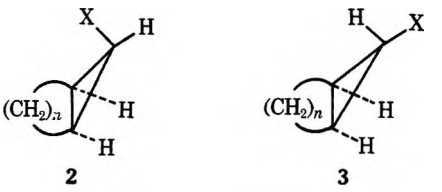
The solvolysis of various monocyclic and bicyclic cyclopropyl compounds has received widespread attention by numerous investigators during the past several years.[1] The impetus for this interest arises, for the most part, from the elegant and far-reaching theories of Woodward, Hoffmann, and DePuy concerning the electrocyclic reactions of cyclopropyl systems.[2] Product as well as kinetic studies have unequivocally demonstrated that in secondary, monocyclic systems (*e.g.*, **1**) electrocyclic opening during



1

X = halogen, -OTs, -OTf

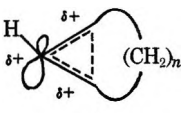
solvolysis proceeds in a concerted disrotatory fashion with the alkyl substituents trans to the leaving group rotating outward and those cis to the leaving group rotating inward.[1,3] These experimental findings are in



2 **3**

X = halogen, -OTs, -OTf

complete agreement with theory.[2] In the bicyclic endo system **2**, again, experiment verifies theory. That is, solvolysis proceeds in a disrotatory fashion affording a cis-allyl cation, which is subsequently quenched by solvent. In the corresponding exo series **3**, experiment seems to support the intermediary of a "partially opened" cyclopropyl cation **4** which leads to cyclo-



4

propyl, cis-allyl, or trans-allyl products (or products derived from trans-allyl derivatives) when $n \leq 5$. The relative yields of these products depend on the magnitude of n and the reaction conditions. For those cases in which $n > 5$ only monocyclic allyl products are obtained, since the ring structure is now large enough to accommodate a transition state approaching that of the monocyclic series.[1,4-7]

Substitution of a group which can stabilize a positive charge at the site of the leaving group (*e.g.*, c-Pr or Ph) results primarily in formation of cyclopropyl prod-

(1) (a) P. v. R. Schleyer, W. F. Sliwinski, G. W. Van Dine, U. Schöllkopf, and J. Paust, *J. Amer. Chem. Soc.*, **94**, 125 (1972), and references contained therein; (b) T. M. Su, Ph.D. Thesis, Princeton University, 1970; (c) W. F. Sliwinski, T. M. Su, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **94**, 133 (1972).

(2) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag Chemie, Weinheim/Bergstr., Germany, 1970.

(3) P. v. R. Schleyer, T. M. Su, M. Saunders, and J. C. Rosenfeld, *J. Amer. Chem. Soc.*, **91**, 5174 (1969).

(4) G. H. Whitham and M. Wright, *Chem. Commun.*, 294 (1967).

(5) U. Schöllkopf, K. Fellenberger, M. Patsch, P. v. R. Schleyer, T. M. Su, and G. W. Van Dine, *Tetrahedron Lett.*, 3639 (1967).

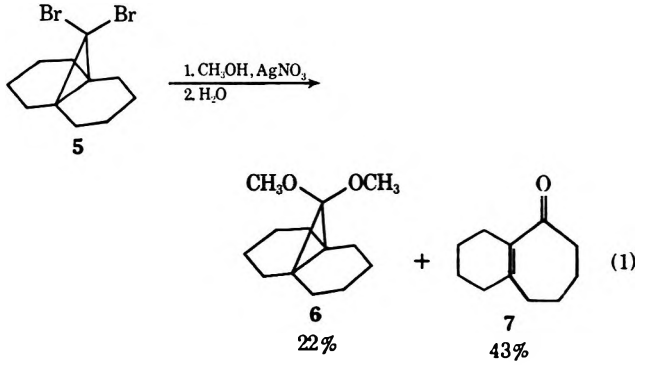
(6) D. T. Clark and G. Smale, *J. Chem. Soc.*, 1050 (1969).

(7) D. Schober, Ph.D. Thesis, University of Chicago, 1969.

ucts.[6-10] Evidence has been presented which is consistent with the formation of a cyclopropyl cation intermediate in these cases.[6]

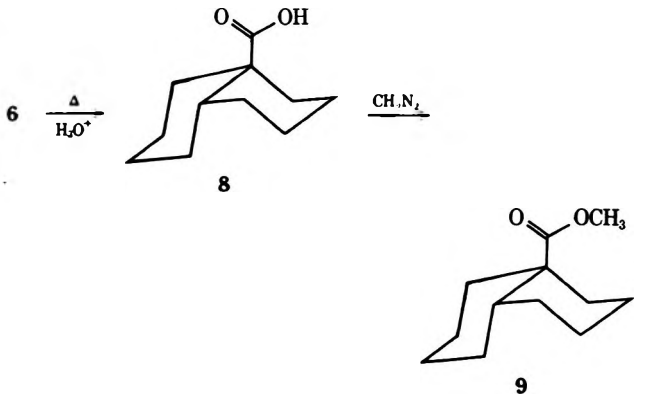
In this paper we report the products obtained in the silver ion assisted methanolysis of the title compound **5**. Compound **5** is constructed such that disrotatory ring opening to a fully opened allyl cation is prohibitive. In addition the electron-withdrawing effect of an α-bromo substituent is not conducive to the stabilization of a cyclopropyl cation. It was conceived that these effects acting in concert would force the system to undergo a Wagner–Meerwein rearrangement, a reaction pathway which heretofore has not been observed in the solvolysis of cyclopropyl derivatives with the leaving group bound directly to the ring.[11]

Compound **5** was synthesized by previously published methods.[13] Its melting point and infrared spectrum were identical with those of an authentic sample.[14] Treatment of **5** with methanolic silver nitrate, followed by an aqueous work-up, resulted in the formation of two major volatile products, **6** and **7**, and several minor components whose structures have not been elucidated (eq 1).



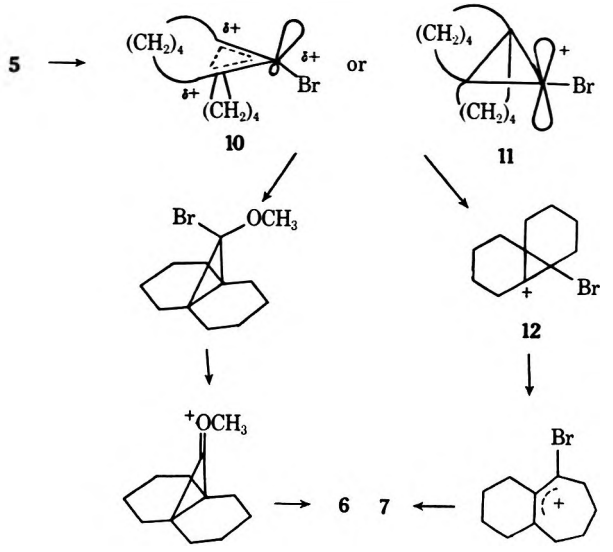
The structure of compound **6** was assigned initially on the basis of its nmr and infrared spectrum in addition to a correct elemental analysis. Unambiguous chemical proof of structure was obtained as outlined in Scheme I. An infrared spectrum of **9** was identical with that of an authentic sample.[15] The structure of compound **7** was assigned on the basis of spectral evidence, a correct elemental analysis, and a molecular ion at m/e 164 in the mass spectrum. The nmr spectrum of **7** exhibits absorption at 1.3–1.8 (multiplet, eight protons) and 1.8–2.6 ppm (multiplet, eight protons). No vinyl absorption was observed. In addition the infrared spectrum of **7** exhibits absorption at 1660 and 1630 cm^{-1} (characteristic of C=C—C=O).[16]

SCHEME I



Whether the products obtained in this study arise from a discrete cyclopropyl cation **11** or a partially opened cation **10** we cannot say at this point; however, current theory would seem to favor the latter.[1] The formation of **7** can be rationalized as arising through a Wagner–Meerwein rearrangement of the initially formed cationic species to a more stable cation which (lacking the steric constraints placed on **10** or **11**) undergoes disrotatory ring opening to the cis allyl ion **12**, the precursor to **7** (see Scheme II). Our initial conjecture concerning the feasibility of a Wagner–Meerwein rearrangement thus seems to be correct for this particular system.

SCHEME II[18]



(8) D. B. Ledlie and E. A. Nelson, *Tetrahedron Lett.*, 1175 (1969).

(9) D. B. Ledlie and W. H. Hearne, *ibid.*, 4837 (1969).

(10) J. A. Landgrebe and L. W. Becker, *J. Amer. Chem. Soc.*, **90**, 395 (1968).

(11) Applequist has reported a possible mechanism for the deamination of spiropentylamine which involves a Wagner–Meerwein rearrangement of the type we have reported. However, in light of the current theory of electrocyclic reactions this seems unlikely.[12]

(12) D. E. Applequist, and G. F. Fanta, *J. Amer. Chem. Soc.*, **82**, 6393 (1960).

(13) R. Vaidyanathaswamy and D. Devaprabhakana, *Chem. Ind. (London)*, **16**, 515 (1968).

(14) W. R. Moore, private communication.

(15) We are indebted to Professor F. D. Greene for supplying us with an infrared spectrum of compound **9**.

(16) Numerous attempts were made to dehydrogenate *trans*-bicyclo-[5.4.0]undecan-2-one with both selenium dioxide and seleneous acid (in various solvents) using the method of Ginsburg in an attempt to synthesize an authentic sample of **7**.[17] However, all our efforts met with failure. We feel, however, that the structure assigned on the basis of the above evidence and mechanistic considerations is unambiguous.

(17) D. Ginsburg and W. J. Rosenfelder, *Tetrahedron*, **1**, 3 (1957).

(18) Both **12** and **13** are depicted as localized cyclopropyl cations since both are tertiary and stabilized in relation to **10**.

(19) Infrared spectra were determined with a Perkin-Elmer Model 457 recording spectrophotometer. The nmr spectra were measured at 60 Hz with an Hitachi Perkin-Elmer R20 spectrometer using tetramethylsilane as an internal reference. All spectra were measured in carbon tetrachloride unless otherwise stated. Magnesium sulfate was employed as the drying agent. All reactions involving air- or moisture-sensitive compounds were carried out under a nitrogen atmosphere.

Experimental Section[19]

11,11-Dibromotricyclo[4.4.1.0^{1,6}]undecane (5).—Compound **5** was prepared according to previously published procedures,[13] mp 43–44° (pentane).[14]

Silver Ion Assisted Methanolysis of 5.—Compound **5** (0.49 g, 1.65 mmol) was added to a solution of silver nitrate (0.6 g, 3.30 mmol) in 50 ml of methanol. The resulting solution was then

stirred for 12 hr at room temperature. The reaction mixture was filtered (removal of AgBr), and water was added to the filtrate. The resulting mixture was extracted with 3 × 25 ml of pentane; the extracts were dried and concentrated to yield 0.32 g of a light yellow oil which was subjected to gas chromatographic analysis (vpc). Two major components (**6** and **7**) were shown to be present which were collected.

Compound **7** exhibited nmr and infrared absorption consistent with the assigned structure as well as a molecular ion in the mass spectrum at *m/e* 164. (see text).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.23; H, 9.86.

An nmr spectrum of **6** exhibits absorption at 3.18 (singlet, six protons) and 1.00–2.01 ppm (multiplet, 16 protons)

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.23; H, 10.55. Found: C, 74.08; H, 10.56. The absolute yields of **6** and **7** were determined by vpc to be 22 and 43%, respectively.[20]

Acid Hydrolysis of 11,11-Dimethoxybicyclo[4.4.1.0^{1,6}]undecane (6).—Compound **6** (50 mg, 2.58 mmol) was dissolved in 50 ml of 75% aqueous dioxane with a trace of *p*-toluenesulfonic acid. The resulting solution was refluxed for 3 days. A gas chromatogram of the reaction mixture containing an internal standard, showed that 75% of the starting material had been consumed, and that none of **7** had been formed. The reaction mixture was basified and extracted with ether. The ether extracts were dried and concentrated to afford a light brown solid whose infrared spectrum was characteristic of a carboxylic acid (**8**).

Esterification of Crude Acid 8.—The crude solid obtained above was dissolved in 50 ml of ether and cooled to 0°. Diazomethane in ether was added dropwise with stirring to the cooled solution until a yellow color persisted. Cold, dilute acetic acid was then added to decompose the excess diazomethane and the reaction was worked up in the usual manner. A yellow oil was obtained which exhibited a single peak on gas chromatographic analysis. The material was collected and its infrared spectrum measured. It was identical with an authentic sample of methyl *cis*-9-decalyl carboxylate.[15]

Registry No.—**5**, 20564-71-0; **6**, 34201-85-9; **7**, 27332-61-2.

Acknowledgment.—Acknowledgment is made to the Research Corporation for support of this research.

(20) A 3 ft × 0.25 in. 10% Carbowax 20M column was employed. Biphenyl was used as the internal standard.

A Novel Cyclization Mediated by Organocopper Reagents

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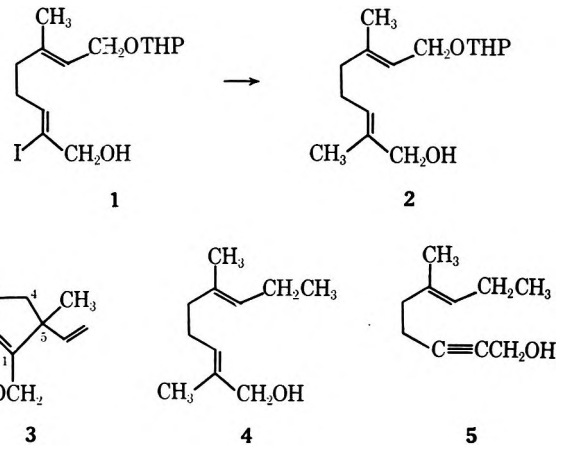
During the course of a synthesis of sirenin,[1] it was observed that the exposure of the iodo ether **1** to dimethylcopperlithium produced in addition to the expected[2] methylation product **2** (30% yield) three other compounds. These by-products, which account for 60% of the mass balance and which appear as a single spot by thin layer chromatography (R_f slightly higher than **2**), have been separated by gas chromatography and identified by spectral methods as **3**, **4**, and **5** (ratio 50:45:5, respectively). The formation of the latter two products is interesting since tetrahydropyranyl ethers, which are normally not regarded as good anionic leaving groups and which are commonly used for protection in organometallic reactions, participate in cross coupling[3] with organocopper reagents. The allylic nature of the tetrahydropyranyl ether **1** must be at least partially responsible for this reactivity.[4] It is also possible that the free hydroxyl group in **1** may play an important role since its conversion to alkoxide might cause tight complex formation with the organometallic reagent or aggregate and so induce a reaction which would normally occur only slowly or not at all. Of even greater significance, however, is the cyclization to the cyclopentene derivative **3**, which is a novel and highly provocative process, and certainly deserving of



further investigation. In a formal sense this cyclization is an intramolecular vinyl–allyl coupling, and as such it may prove to have significant generality.[5,6]

Experimental Section

Reaction of Dimethylcopperlithium with 2-Iodo-6-methyl-(2′-tetrahydropyranyloxy)-*trans,trans*-2,6-octadien-1-ol (1).—A flask containing 1.95 g (10.32 mmol) of cuprous iodide was flushed thoroughly with nitrogen and placed in an ice bath, and 75 ml of ether was added. Methyllithium (20.55 mmol, 12.7 ml of a 1.62 *M* ether solution) was added over a 5-min period, and stirring was continued for 10 min after addition was complete. 2-Iodo-6-methyl-8-(2′-tetrahydropyranyloxy)-*trans,trans*-octadien-1-ol (**1**) (300 mg, 0.825 mmol) in 3 ml of ether was added, and the reaction vessel was placed in a 5° cold room and stirred for 30 hr, during which time the reaction mixture changed in color from pale yellow to dark green. The solution was poured over ice–water (considerable bubbling) and filtered through a pad of Celite 545 to remove insoluble copper salts, and the organic layer, combined with four extracts of the aqueous layer, was dried over sodium carbonate (and briefly over $MgSO_4$), filtered, and concentrated to *ca.* 160 mg of an oil. This crude product showed spots of R_f 0.72 and 0.36 on analytical tlc (1:1 hexane–ether, two developments), and these two components were separated by preparative tlc (pH 8, 1:1 hexane–ether). The more polar material thus isolated (62 mg, 30%) was identified as the expected methylation product **2**, since spectral and analytical data for it were identical with those of authentic **2** prepared by an alternative procedure.[1]

Gas chromatographic (gc) analysis (Carbowax 20M column

(1) See E. J. Corey, K. Achiwa, and J. A. Katzenellenbogen, *J. Amer. Chem. Soc.*, **91**, 4318 (1969).

(2) E. J. Corey and G. H. Posner, *ibid.*, **89**, 3911 (1967).

(3) See, for example, (a) E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *ibid.*, **89**, 4245 (1967); (b) E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *ibid.*, **90**, 5618 (1968).

(4) Epoxides and allylic acetates have also been found to react readily with organocopper reagents. See (a) R. J. Anderson, C. A. Henrick, and J. B. Siddall, *ibid.*, **92**, 735 (1970); (b) P. Roma and P. Crabbe, *ibid.*, **91**, 3289 (1969); (c) R. J. Anderson, *ibid.*, **92**, 4978 (1970); R. W. Herr, D. M. Wieland, and C. R. Johnson, *ibid.*, **92**, 3813 (1970).

(5) For other recently discovered cyclization reactions using organocopper reagents, see (a) E. J. Corey and I. Kuwajima, *ibid.*, **92**, 395 (1970), and (b) E. J. Corey, M. Narisada, T. Hiraoka, and R. A. Ellison, *ibid.*, **92**, 396 (1970).

(6) This study was assisted financially by the National Institutes of Health and the National Science Foundation.

at 125°) of the less polar fraction obtained in the preceding reaction showed three components with retention times of 2.3 min (45%, component A), 5.7 min (50%, component B), and 9.2 min (5%, component C). These materials were separated by preparative gc (Carbowax 20M + KOH column at 180°) and were assigned structures **3**, **4**, and **5** on the basis of spectral data (obtained for gas chromatographically homogeneous samples): component A, 1-hydroxymethyl-5-methyl-5-vinylcyclopentene (**3**); component B, 2,6-dimethyl-*trans*,*trans*-2,6-nonadien-1-ol (**4**); and component C, 6-methyl-*trans*-6-nonen-2-yn-1-ol (**5**).

The alcohol **3** showed the following nmr spectrum (CCl_4): 1.15 (singlet, 3 H, CH_3–), 1.55–1.95 (multiplet, 2 H, $-CH_2-$, C-4), 2.1–2.45 (multiplet, 2 H, $-CH_2-$, C-3), 3.78 (singlet, 1 H, –OH), 3.94 (broad singlet, 2 H, $-CH_2O-$), 4.90 (doublet, J = 18 Hz, 1 H, –CH=C(H)H, cis to cyclopentene ring), 4.90 (doublet, J = 10 Hz, 1 H, –CH=C(H)H, *trans* to cyclopentene ring), 5.60 (1 H, =CH–, C-2), and 5.81 (doublet of doublets, J = 10, 18 Hz, 1 H, $-CH=CH_2$). The ir spectrum (CCl_4) exhibited bands at 3.05 (s, O–H stretch), 3.40 and 3.50 (s, C–H stretch), 6.10 (m, C=C stretch), 6.90, 7.10, and 7.30 (m, C–H bend), 9.15 (m), 9.70 (s, C–O stretch), 9.95 and 10.9 (s, C–H out of plane deformation, $-CH=CH_2$), and 12.65 (m). The mass spectrum (20 eV) showed a molecular ion at m/e 138, with prominent peaks resulting from cleavage of the fragments CH_3 (123), H_2O (120), CH_2OH (107), and H_2O + CH_3 (105), as well as other peaks at m/e 96, 94, 92, and 79.

An exact mass determination (AEI MS-9 mass spectrometer) showed the parent peak at m/e 138.1040 (calcd for $C_9H_{14}O$: 138.1044).

The nmr spectrum (CCl_4) of **4** exhibited signals at 0.94 (triplet, J = 7.5 Hz, 3 H, CH_3CH_2-), 1.60 (singlet, 6 H, $CH_3C=$), 1.75–2.3 (multiplet, 6 H, $-CH_2-$, C-4, 5, 8), 2.49 (singlet, 1 H, –OH), 3.85 (singlet, 2 H, $-CH_2O-$), 5.09 (triplet, J = 6 Hz, 1 H, =CH–, C-7), and 5.31 (triplet, J = 6 Hz, 1 H, =CH–, C-3). The ir spectrum (liquid film) revealed bands at 3.00 (s, O–H stretch), 3.40 and 3.50 (s, C–H stretch), 5.98 (w, C=C stretch), 6.90 and 7.20 (m, C–H bend), 7.65 (w), 8.20 (w), 8.65 (w), 9.30 (m), 9.85 (s, C–O stretch), and 11.60 (m).

The nmr spectrum (CCl_4) of **5** exhibited resonances at 0.94 (triplet, J = 7.5 Hz, 3 H, CH_3CH_2-), 1.60 (singlet, 3 H, $CH_3C=$), 1.8–2.4 (multiplet, 7 H, $-CH_2-$, C-4, 5, 8, and –OH), 4.11 (singlet, 2 H, $-CH_2O-$), and 5.14 (triplet, J = 6 Hz, 1 H, =CH–). The ir spectrum (liquid film) displayed absorbence maxima at 3.0 (s, O–H stretch), 3.40 and 3.50 (s, C–H stretch), 4.37 and 4.40 (w, C≡C stretch), 6.00 (w, C=C stretch), 6.90 and 7.25 (m, C–H bend), 8.15 (m), 8.80 (s), and 9.80 (s, C–O stretch).

Registry No.—**1**, 33835-56-2; **3**, 33835-15-3; **4**, 33835-57-3; **5**, 33835-58-4; dimethylcopperlithium, 15681-48-8.

Mechanism of the Base-Catalyzed Condensation of Naphthols with 2,3-Dichloro-1,4-naphthoquinone

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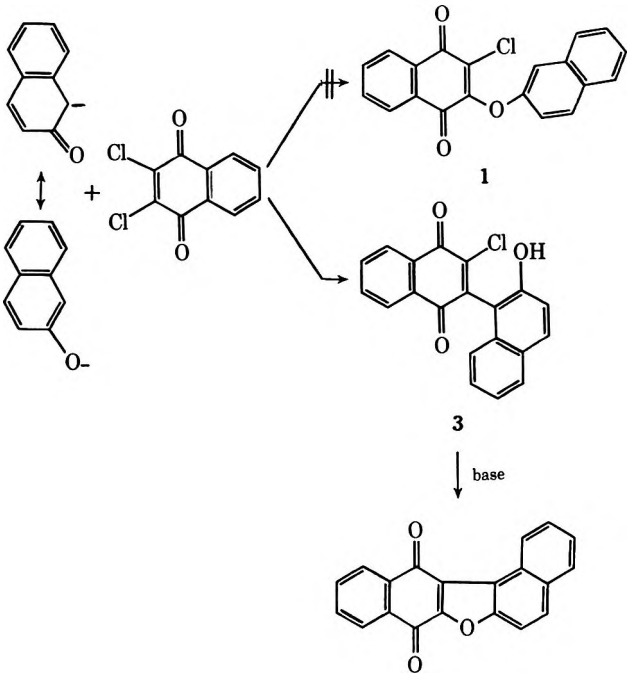
Dinaphthofurandiones, more commonly called benzobrazanquinones, are a series of heterocyclic quinones derived from the base-catalyzed condensation of 1- or 2-naphthol with 2,3-dichloro-1,4-naphthoquinone (DCNQ). The synthesis of dinaphthofurandiones has been reported[1,2] to proceed *via* initial O alkylation of the naphthol anion to yield compound **1**, in the case of 2-naphthol, which then cyclizes, under the reaction conditions, to provide dinaphtho[2,1:2′,3′]furan-8,13-dione (**2**).

Since the reported cyclization of **1** to **2** did not appear reasonable and consistent with the poorly nucleophilic character of the one position of the naphthyl ether, the base-catalyzed condensation of 2-naphthol with DCNQ was investigated.

A red crystalline compound was isolated from the reaction of 2-naphthol with DCNQ in 2-propanol, using 1 mol of sodium acetate, and was proven to be the intermediate by the cyclization to **2** in refluxing pyridine. The intermediate displays an OH stretching frequency at 3575 cm^{-1} in dioxane and treatment of an aqueous acetone solution with alkali produces a blue-colored anion [λ_{max} = 670 mμ ($\epsilon \sim 4000$)], which converts to compound **2** after several minutes at room temperature. Compound **2** decomposes under these basic conditions in a secondary process, providing 2-naphthol and several other compounds which were not identified.

Thus, the intermediate is indicated to be the product of C alkylation (**3**) where a route for ring closure and dinaphthofurandione formation is clearly provided.



Dinaphthofurandione formation then involves initial alkylation on the 2-naphthol anion one position rather than an oxygen, consistent with the greater nucleophilicity of C *vs.* O bases in polar solvents.[3]

This mechanism is also consistent with the inability to form benzo[*b*]naphtho[2,3-*d*]furan-6,11-dione from the condensation of phenol with DCNQ[4] and also the ease of the preparation of certain substituted benzonaphthofurandiones in which meta-substituted phenols are condensed with DCNQ.[2] In these cases strongly electron-donating substituents such as methoxy or dimethylamino, which favor C alkylation, must be employed. If condensation occurs initially by heteroatom attack, as in the case of the addition of aniline to

(1) R. V. Acharya, B. D. Tilak, and M. R. Venkiteswaran, *J. Sci. Ind. Res.*, **16B**, 400 (1957).

(2) M. F. Sartori, *Chem. Rev.*, **63**, 279 (1963).

(3) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 259.

(4) R. Gruber, private communication.

DCNQ, cyclization does not occur unless another mechanism is offered (*e.g.*, Ullman reaction).

While this investigation had dealt solely with the base-catalyzed condensation of 2-naphthol with DCNQ, these mechanistic aspects may be generally applicable to other hydroxy aromatic systems.

Experimental Section[5]

Preparation of 1-[2-(3-Chloro-1,4-naphthoquinone)]-2-naphthol (3).—A suspension of 2-naphthol (1.44 g, 0.01 mol), DCNQ (2.27 g, 0.01 mol), and sodium acetate (0.82 g, 0.01 mol) in 2-propanol (50 ml) was heated at reflux for 10 hr. The originally yellow solution turned red shortly after heating commenced. The red solution was allowed to cool to room temperature and a red, crystalline solid was collected by suction filtration. Recrystallization from 2-propanol provided 1.2 g (36%) of **3** as red needles, mp 178–179°, ir (dioxane) 3575 (OH), 1675 cm^{-1} (C=O).

Anal. Calcd for $C_{20}H_{11}O_3Cl$: C, 71.76; H, 3.31; Cl, 10.59. Found: C, 71.45; H, 3.20; Cl, 10.51.

Preparation of Dinaphtho[2,1:2′,3′]furan-8,13-dione (2) from Compound 3.—Compound **3** (0.490 g, 1.49 mmol) was refluxed for 2 hr in pyridine (25 ml) and the solution was allowed to cool to room temperature. The yellow-orange crystalline compound, which crystallized from the pyridine solution, was then collected by suction filtration. Compound **2**, 0.31 g (67%, mp 272–273° (lit.[2] mp 271–272°), was obtained after recrystallization from 2-propanol.

Registry No.—**3**, 33835-18-6; 2,3-dichloro-1,4-naphthoquinone, 117-80-6.

Acknowledgment.—Technical assistance by Richard L. Schank and discussions with W. H. H. Gunther, B. Grushkin, R. J. Gruber, and H. A. Six are gratefully acknowledged.

(5) Melting points are uncorrected. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were recorded on a Perkin-Elmer 247 grating spectrophotometer.

Reaction between Arylnitrones and Arylnitroso Compounds

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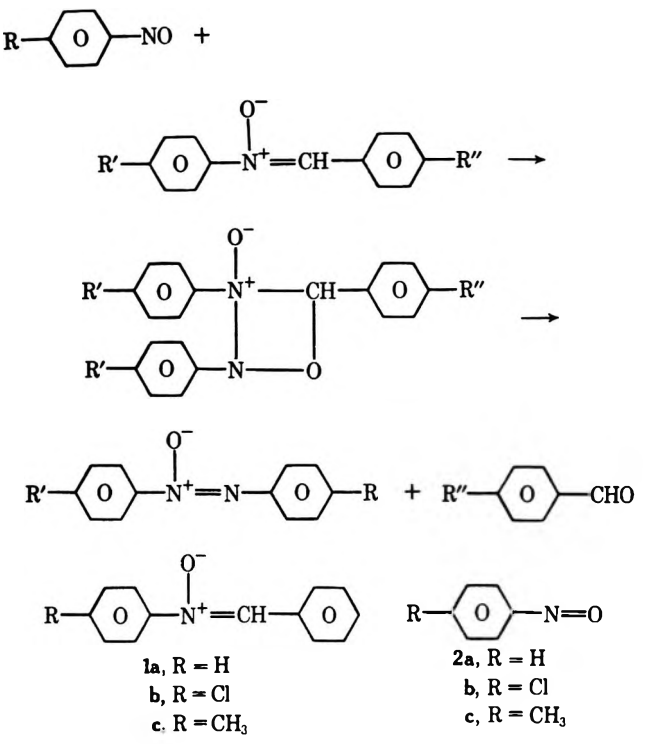
For another study we required a number of *p,p′*-disubstituted azoxybenzenes. The few reported methods for the synthesis of pure isomers[1a,b] were not entirely suitable for the preparation of the desired compounds, and we were interested in finding a more general procedure.

Alessandri[2] reported the formation of azoxybenzene in the reaction between nitrosobenzene and a nitrone. In a recent publication, Taylor and Buntrock[3] postulated a cyclic intermediate in a similar reaction which

SCHEME I



suggested the reaction mechanism shown in Scheme I. This reaction appeared to be a potentially attractive route to unsymmetrically substituted azoxybenzenes.

In our investigation of the reaction between nitrosobenzene and *N*,α-diphenylnitrone, we found that the reaction went to completion in untreated chloroform after several hours at ambient temperature, but that no reaction occurred in dimethylformamide, dimethyl sulfoxide, acetonitrile, or benzene under the same conditions.[4] We also found that the reaction was catalyzed by trifluoroacetic acid in all solvents and that the reaction was inhibited in dry, acid-free chloroform.

The reactions between nitrones (**1**) and nitrosobenzenes (**2**) were conducted in untreated chloroform, presumably containing a catalytic amount of acid. Column chromatography (alumina) of the products of the reaction of **1b** and **2a** gave three fractions, which were identified by comparison with authentic samples as azoxybenzene, 4,4′-dichloroazoxybenzene, and a mixture of 4- and 4′-chloroazoxybenzene in the ratio of 0.9:0.9:1. The reactions between **1a** and **2b** yielded the same product ratio, indicating that both reactions proceeded through the same intermediates.

Similar results were obtained for the reactions of **1c** and **2a** and **1a** with **2c**. The three isolated fractions were azoxybenzene, 4,4′-dimethylazoxybenzene, and a mixture of 4- and 4′-methylazoxybenzene in the ratio of 0.95:0.96:1.

Reactions between *p*-chlorophenylhydroxylamine and **2a** in chloroform gave the same distribution of azoxy products as in the reaction between **1b** and **2a**. Similar results were obtained in the reaction between *p*-methylphenylhydroxylamine and **2a** in chloroform.

These results rule out the cyclic mechanism shown in Scheme I. A more plausible mechanism involves the acid-catalyzed hydrolysis of nitrone to give the phenyl-

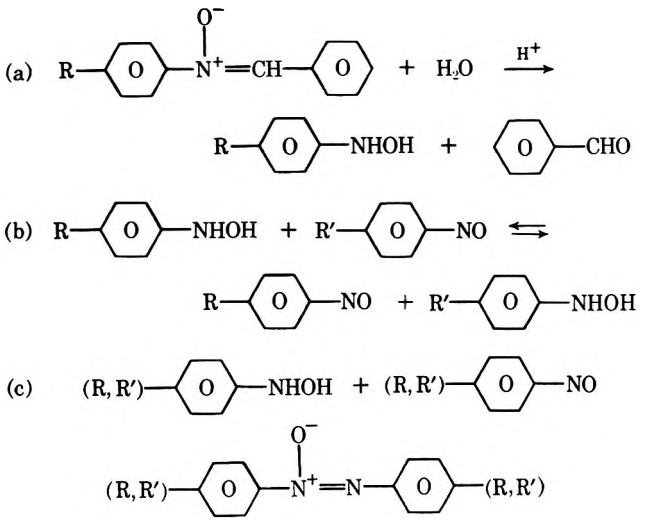
(1) (a) T. E. Stevens, *J. Org. Chem.* **29**, 311 (1964). (b) L. C. Behr, E. G. Alley, and O. Livand, *ibid.*, **27**, 65 (1962).

(2) L. Alessandri, *Gazz. Chim. Ital.*, **54**, 426 (1924).

(3) E. C. Taylor and R. E. Buntrock, *J. Org. Chem.*, **36**, 634 (1971).

(4) Previous authors conducted their reactions in chloroform. See ref 2 and 3.

SCHEME II



hydroxylamine which then equilibrates with the phenylnitrosobenzene. The phenylhydroxylamines and phenylnitroso compounds then react irreversibly to give azoxy products (Scheme II). The kinetics and mechanism of the latter reactions have previously been investigated.[5a,b]

In order to examine the possibility that α-anilino-*N*-phenylnitrones[3] might react differently than **1**, α-*p*-toluidino-*N*-tolylnitrone (**3**) was treated with nitrosobenzene in chloroform in the dark for 5 days at ambient temperature. In addition to *p*-methylformanilide, azoxybenzene, 4,4′-dimethylazoxybenzene, and a mixture of 4- and 4′-methylazoxybenzene were formed. This suggests that the α-anilino-*N*-phenylnitrones react *via* a mechanism similar to α-phenyl-*N*-phenylnitrones (Scheme II).

Experimental Section

The aryl hydroxylamines were prepared by the procedure of Kamm.[6] Nitrosobenzene was purchased from the Aldrich Chemical Co. The other nitrosobenzenes were prepared using the procedure of Barrow.[7] α-*p*-Chlorophenyl-*N*-phenylnitrone and α-*p*-tolyl-*N*-phenylnitrone were synthesized using the reported methods.[8a,b]

α-*p*-Toluidino-*N*-*p*-tolylnitrone.—Using the procedure of Taylor,[3] a solution of *p*-methylnitrosobenzene (2.4 g, 0.92 mol) and *p*-methylmethylene aniline (3.6 g, 0.03 mol) in 70 ml of chloroform was stoppered and kept in the dark for 70 hr. The chloroform was removed under reduced pressure. The solid remaining was taken up and recrystallized from benzene, yield 1.9 g (35%), mp 129–130°.

Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.96; H, 6.71; N, 11.66. Found: C, 74.77; H, 6.79; N, 11.42.

The reaction below illustrates the general procedure used in the reactions of arylnitrones with the nitrosobenzenes.

Reaction of α-Phenyl-*N*-*p*-chlorophenylnitrone with Nitrosobenzene.—A solution of α-phenyl-*N*-*p*-chlorophenylnitrone (3.45 g, 0.015 mol) and nitrosobenzene (1.5 g, 0.015 mol) in 75 ml of chloroform was stoppered and placed in the dark for 70 hr. At the end of that time no nitrone remained as evidenced by glpc. Three products were formed. The products were separated by preparative glpc and found to be azoxybenzene, 4- and 4′-chloroazoxybenzene, and 4,4′-dichloroazoxybenzene by superimposing their ir spectra with the ir spectra of known samples. The three products were formed in the ratio of 0.9:1:0.9. Benzaldehyde was the only other product formed.

Reaction of α-*p*-Toluidino-*N*-*p*-tolylnitrone with Nitrosobenzene.—Using the procedure of Taylor and Buntrock,[3] a mixture of α-*p*-toluidino-*N*-*p*-tolylnitrone (0.48 g, 0.0002 mol) and nitrosobenzene (0.22 g, 0.002 mol) in 30 ml of chloroform was allowed to stand in the dark for 5 days. Analysis by glpc showed that the nitrone was 75% reacted. The four products found were *p*-methylformanilide, azoxybenzene, 4- and 4′-methylazoxybenzene, and 4,4′-dimethylazoxybenzene, formed in the ratio of 7:3:1.8:1.

Registry No.—α-*p*-Toluidino-*N*-*p*-tolylnitrone, 33905-35-0; α-phenyl-*N*-*p*-chlorophenylnitrone, 5909-74-0; nitrosobenzene, 586-96-9.

(5) (a) Y. Ogata, M. Tsuchida, and Y. Takgi, *J. Amer. Chem. Soc.*, **79**, 3397 (1957). (b) G. A. Russell and E. J. Geels, *ibid.*, **87**, 122 (1965).

(6) O. Kamm, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., p 445.

(7) F. Barrow and F. J. Thorneycroft, *J. Chem. Soc.*, 773 (1939).

(8) (a) R. E. Erickson and T. M. Myszkewicz, *J. Org. Chem.*, **30**, 4236 (1965). (b) S. L. Larsen, G. Schroll, S. O. Lawesson, J. H. Bowie, and R. G. Cooks, *Tetrahedron*, **24**, 5193 (1968).

On the Friedel–Crafts Benzoylation and Acylation of Kojic Acid

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Received June 16, 1971

Despite reports to the contrary, we believe that Friedel–Crafts acylation or aroylation reactions of kojic acid (**1**, 2-hydroxymethyl-5-hydroxy-4*H*-pyran-4-one)[1] under Friedel–Crafts conditions are yet to be accomplished.

Woods reported that treatment of **1** with benzoyl chloride and aluminum chloride in carbon disulfide yielded 6-benzoylkojic acid (**2**), mp 188°.[2] Following the published procedure, we obtained a crystalline monobenzoylated product, mp 180–181°, mol wt 264 (mass spectrum), which gave a positive $FeCl_3$ test. That it was not the anticipated Friedel–Crafts product but rather the benzoate ester **3** (lit.[3] mp 180–181°) was demonstrated by comparing the nmr spectra of **1** and **3**, which showed the deshielding of the methylene protons from 4.50 to 5.20 ppm by the benzoate group, and which confirmed the presence of two pyrone ring protons (Table I). Although the signals for the phenyl protons overlapped that of the C-6 proton, the latter was clearly visible in the integration.

Woods' structural assignment for his benzoylated product rested largely on the results of a Clemmensen reduction, which yielded a product different from the starting material, and the reaction was therefore taken to represent the reduction of the benzoyl ketone. While it is entirely possible that Woods had actually obtained **2**, and that its synthesis was very sensitive to minor changes in reaction conditions, we also considered the possibility that he was dealing with **3** and that its reduction had taken an unforeseen course. Treatment of **3** in the conditions of the Clemmensen reduction[1] yielded some benzoic acid, probably resulting from hydrogenolysis.[3] A neutral fraction which we could not crystallize was also obtained. It was acetylated to yield a product, mp 91–92°. Its molecular weight of 168 (mass spectrum) and nmr ($CDCl_3$), which consisted

(1) A. Beelik, "Advances in Carbohydrate Chemistry," Vol. 11, M. L. Wolfrom, Ed., Wiley, New York, N. Y., 1956, p 145.

(2) L. L. Woods, *J. Amer. Chem. Soc.*, **74**, 1105 (1952).

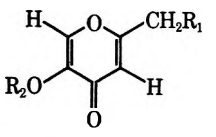
(3) A. Beelik and C. B. Purves, *Can. J. Chem.*, **33**, 1361 (1955).

TABLE I

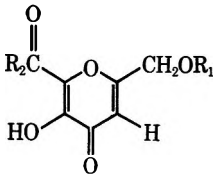
NMR SPECTRA OF KOJIC ACID DERIVATIVES[a]

Compd	Solvent	$-CH_2R$	H-3	H-6	Phenyl	CH_3CO	OCH_3	OH
1	DMSO-d_6	4.50	6.60	8.10				5.68
								9.09
3	DMSO-d_6	5.20	6.60	*b*	7.70–8.20[b]			9.30
4	$CDCl_3$	2.27	6.23	7.73		2.27		
5	$CDCl_3$	2.30	6.27	7.80				
	DMSO-d_6	2.34	6.32	8.08				9.05
6	$CDCl_3$	5.12	6.55	*b*	7.30–8.20[b]	2.32		
7	$CDCl_3$	4.93	6.53	7.92		2.17		
						2.33		
8	$CDCl_3$	5.03	6.68	*b*	7.40–8.40[b]	2.20		
9	$CDCl_3$	5.28	6.68	*b*	7.30–8.40[b]			
	DMSO-d_6	5.41	7.20	8.85	7.50–8.40[b]			
12	$CDCl_3$	4.93	6.50	7.87		2.17		
	DMSO-d_6	5.00	6.53	8.20		2.13		9.00
13	DMSO-d_6	4.35	6.36	8.18			3.69	5.70
14	$CDCl_3$	4.95	6.49	7.65		2.17	3.80	
15	DMSO-d_6	4.67	7.70	8.13				9.26
16	DMSO-d_6	4.40	6.55	8.74	7.60–8.40			5.84

[a] Values in parts per million relative to internal TMS. [b] The phenyl signals overlapped H-6.



1, R_1 = OH; R_2 = H
3, R_1 = $OCOC_6H_5$; R_2 = H
4, R_1 = H; R_2 = $OCOCH_3$
5, R_1 = R_2 = H
6, R_1 = $OCOC_6H_5$; R_2 = $COCH_3$
7, R_1 = $OCOCH_3$; R_2 = $COCH_3$
8, R_1 = $OCOCH_3$; R_2 = COC_6H_5
9, R_1 = $OCOC_6H_5$; R_2 = COC_6H_5
12, R_1 = $OCOCH_3$; R_2 = H
13, R_1 = OH; R_2 = CH_3
14, R_1 = $OCOCH_3$; R_2 = CH_3
15, R_1 = Cl; R_2 = H
16, R_1 = OH; R_2 = COC_6H_5



2, R_1 = H; R_2 = C_6H_5
10, R_1 = H; R_2 = CH_3
11, R_1 = $COCH_3$; R_2 = CH_3

of three singlets at 7.73 (1 H), 6.23 (1 H) and 2.27 ppm (6 H), suggested the 2-methyl-5-acetoxypyrone structure **4**. This assignment was confirmed by comparison with an authentic sample prepared from allomaltol (**5**), which was itself conveniently obtained by Clemmensen reduction of 1.[4,5] No reaction was observed when **3** was exposed to thionyl chloride in hexane as described.[1,6] At room temperature **3** did not react with acetyl chloride in benzene, while acetylation took place upon heating, yielding **6**, mp 86–87°. It is therefore probable that Woods' product, mp 182°, was again his starting material. Finally, work-up of the Meerwein–Ponndorf–Verley reduction of **3**, which was carried out as described,[1] yielded crystalline starting material and we did not observe Woods' product, mp 114–115°.

Woods and Dix later noticed that benzoylation of diacetyl kojic acid (**7**) with benzoyl chloride in trifluoroacetic acid yielded a product, mp 143°, which was different from that obtained through benzoylation of **1** followed by acetylation as described above.[7] As no structural explanation had been offered, we repeated the benzoylation of **7**, which gave us a product, mp 145–146°, probably identical with that obtained by Woods and Dix. It was identified as 2-acetoxymethyl-5-benzoxy-4*H*-pyran-4-one (**8**) by its nmr ($CDCl_3$) which showed two pyrone ring protons (one of them overlapped by the phenyl), one acetyl, and the methylene at 4.90 ppm. The alternate 2-benzoxymethyl-5-acetoxy-4*H*-pyran-4-one (**6**) formulation was ruled out by the nmr. Synthesis of **8** and direct comparison confirmed the assignment.

The ring benzoylation to **2** was also claimed by Woods[8] in the reaction of **1** with benzoic acid or ethyl benzoate in the presence of trifluoroacetic acid. The values reported for the products, mp 188 and 186–187°, respectively, agree with that of **3**, which is the product obtained by us when the published procedures were followed.

Woods also reported[1] on the stannic chloride catalyzed benzoylation of **1**, without clarifying the nature of the crystalline product(s).[9] In our hands, benzoylation in these conditions yielded the diester **9**, mp 133–134°, which could survive the described acidic treatment.

We now turn to the Friedel–Crafts acetylation of **1** to **10**. Woods' first report on the matter concerned the reaction with acetic anhydride and zinc chloride at

(4) The reduction of an amino- or hydroxymethyl to a methyl group is not without precedent in the γ-pyrone series. For example see (a) R. L. Miller, B. E. Tate, R. P. Allingham, and H. Rutner, Belgian Patent 625,114 (1963); *Chem. Abstr.*, **60**, 10651 (1964); (b) B. E. Tate, U. S. Patent 3,171,842 (1965); *Chem. Abstr.*, **62**, 16201 (1965); (c) I. Ichimoto, K. Fujii, and C. Tatsumi, *Agr. Biol. Chem.*, **29**, 325 (1965); (d) B. E. Tate and R. P. Allingham, U. S. Patent 3,365,469 (1968); *Chem. Abstr.*, **69**, 10360 (1968).

(5) A similar reduction of a benzoxymethyl to a methyl group was reported by Beelik and Purves.[3]

(6) The product reported by Woods and purported to be 2-chloromethyl-5-hydroxy-6-benzoyl-4*H*-pyran-4-one melted at 185–187°, very close to his starting material (188°).

(7) L. L. Woods and P. A. Dix, *J. Org. Chem.*, **24**, 1126 (1959).

(8) L. L. Woods, *ibid.*, **27**, 696 (1962).

(9) No melting point was reported for the twice-recrystallized material which was submitted to analysis. Its resemblance to the product, mp 128–130°, which was obtained by subsequent acid treatment, is therefore unknown.

elevated temperature.[10] The product, mp 106°, was soon shown by Hurd and Sims[11] to be the diacetate **7**. A later report[12] described the acetylation with acetic anhydride and phosphoric acid at 150°, which was claimed to yield **10**, mp 156.5°, *via* its monoacetate **11**, mp 119–120°. We did not obtain this material, but found instead a product, mp 135–137°, mol wt 184, which was the monoacetate **12** as shown by its nmr (Table I). It behaved as described by Woods, who may have been dealing with an impure sample. He reported that reflux in water converted it into a product, mp 156.5°; reflux of **12** in water hydrolyzed it into kojic acid, mp 155–157°, in agreement with Hurd and Sims,[11] who observed complete hydrolysis of the diacetate **7** when refluxed in water. Complete O acetylation of Woods' compound was reported to yield a product, mp 98–99°; acetylation of **12** (performed more conveniently by complete acetylation of **1** with acetyl chloride) yielded the diacetate **7**, mp 101–102°. Finally, Clemmensen reduction of **12** would now be expected to yield **5**, mp 150–152°, in a reaction analogous to that of **3**, and the product obtained by Woods melted at 147–149°.

A synthesis of 6-acetylkojic acid (**10**), mp 136°, was also claimed by Eiden,[13] who treated **1** with acetic acid in the presence of hydrogen chloride. In our hands the synthesis led to the acetate **12**, and the proposed structures for the thio derivatives[13] must be corrected accordingly.[14] This result is analogous to that described by Ichimoto and Tatsumi, who acetylated **1** with acetic acid and zinc chloride.[15]

Woods also reported the synthesis of diketones when kojic acid or its derivatives were treated with diethyl oxalate in the presence of trifluoroacetic acid.[16] The foregoing results with ethyl benzoate made the claim doubtful, and we found that no reaction took place when **1** was treated as indicated, thus explaining the melting point and yield of Woods' material. A "reductive acetylation" had been performed on that material, yielding a product, mp 103–104°. We found that **1** yielded the diacetate **7**, mp 102–103°, when treated with zinc and acetic anhydride as indicated. A similar observation was made with the methyl ether **13**, which did not react with diethyl oxalate and which yielded the acetate **14**, mp 124–125°, in the presence of zinc and acetic anhydride.[17]

The products obtained by Woods and Dix,[18] after treatment of **1**, **13**, or chlorokojic acid (**15**) with carbon monoxide and hydrogen chloride in trifluoroacetic acid, and the starting materials had very close melting points and had nmr spectra not readily explained by the proposed structures. We found no reaction when the published procedures were followed and the nmr spectra must therefore be reinterpretated in terms of showing the hydroxyl protons in DMSO,[19] rather than ab-

(10) L. L. Woods, *J. Amer. Chem. Soc.*, **70**, 2608 (1948).
(11) C. D. Hurd and R. J. Sims, *ibid.*, **71**, 2440 (1949).
(12) L. L. Woods, *ibid.*, **75**, 3608 (1953).
(13) F. Eiden, *Arzneim.-Forsch.*, **10**, 947 (1960).
(14) It is interesting to note that a similar treatment of 2-hydroxymethyl-3-hydroxy-4*H*-pyran-4-one yielded the chloromethyl derivative.[4a]
(15) I. Ichimoto and C. Tatsumi, *Bull. Univ. Osaka Prefect., Ser. B*, **13**, 53 (1962); *Chem. Abstr.*, **61**, 14627*f* (1964).
(16) L. L. Woods, *Trans. Kans. Acad. Sci.*, **66**, 59 (1963); *Chem. Abstr.*, **59**, 7624*e* (1963).
(17) Woods' sample, mp 102°, may have been the acetate in impure form.
(18) L. L. Woods and P. A. Dix, *J. Org. Chem.*, **26**, 1028 (1961).
(19) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.* **86**, 1256 (1964).

normal aldehyde protons. Judging from these results and our own synthesis with zinc and acid, one would have believed that the borohydride reduction performed by Woods and Dix[18] had converted **1** into **5**, mp 167°. However, we observed no reaction when **1** was treated with sodium borohydride.

Experimental Section

Benzoylation of Kojic Acid with $AlCl_3$.—Woods' procedure[2] was repeated with 14.2 g of **1**. The crude product was recrystallized twice from EtOH to yield 4.2 g of **3**: mol wt 246 (mass spectrum); mp 179–180° (lit.[1] mp 180–181°); ir (Nujol) 3264, 1732, 1640 cm^{-1}. No other product was found when either **1** or **3** was treated as above with excess BzCl.

Clemmensen Reduction of *O*-Benzoylkojic Acid (3).—Woods' procedure was repeated with 4 g of **3** and 30 g of Zn amalgam.[20] The filtrate obtained after a 7-hr reflux period was evaporated to yield a brown oil, which was dissolved in C_6H_6 and washed with Na_2CO_3 and with H_2O. Acid treatment of the aqueous phase yielded 0.712 g of benzoic acid, mp 121–123°, identified by direct comparison. The C_6H_6 solution was evaporated under vacuum and yielded a dark brown oil which did not crystallize. It was treated with excess Ac_2O–pyridine and was chromatographed over silica gel. Elution with $CHCl_3$–EtOAc (1:1) gave 0.2 g of **4**, mol wt 168 (mass spectrum), mp 91–92°, after recrystallization from CCl_4.

2-Benzoxymethyl-5-acetoxy-4*H*-pyran-4-one (6).—No reaction was observed (melting point and nmr) when a mixture of 1 g of **3** and 3 ml of AcCl in 20 ml of C_6H_6 was allowed to stand for 24 hr at room temperature. When the above mixture was refluxed for 2 hr and evaporated under vacuum a solid was obtained, which was recrystallized twice from EtOH to yield 0.26 g of **6**, mp 86–87°.

Reaction of 3 with $SOCl_2$.—A mixture of 1 g of **3** and 3 ml of $SOCl_2$ in 15 ml of hexane was stirred for 24 hr at room temperature. After filtration, the solid was washed with hexane. It was identical with the starting material (melting point and nmr).

Meerwein–Ponndorff–Verley Reduction of 3.—A mixture of 2 g of **3** and 3 g of $Al[OCH(CH_3)_2]_3$ in 40 ml of 2-propanol was refluxed for 8 hr. After removal of the solvent, the residue was acidified with 10 ml of concentrated HCl and 50 ml of H_2O was added. Extraction with C_6H_6 yielded a solid which was boiled with 100 ml of H_2O for 15 min and recrystallized from EtOH to yield 0.301 g, mp 186–188°, identical with starting material.[21]

Reduction of Kojic Acid to Allomaltol (5).—The procedure used for the reduction of hydroxymaltol to maltol[4a] was followed. It yielded 60% of **5**, mol wt 125 (mass spectrum), subliming near 130°, mp (capillary) 150–152° (lit.[1] mp 166°).

Acetylallomaltol (4).—A mixture of 0.1 g of **5** and 78 mg of AcCl in 25 ml of $CHCl_3$ was refluxed for 3 hr. The product was recrystallized twice from CCl_4 to yield 0.1 g of crystals, mp 92–93° identical with the product of the Clemmensen reduction of **3**.

2-Acetoxymethyl-5-benzoxy-4*H*-pyran-4-one (8).—A solution of 2 g of **7** and 1.5 ml of benzoyl chloride in 10 ml of CF_3COOH was refluxed for 1 hr. It was poured over ice and the solid was recrystallized from EtOH to yield 0.503 g of **8**: mp 145–146° (lit[3] mp 144°); ir ($CHCl_3$) 1730, 1640, and 1620 cm^{-1}. The product was identical with a sample prepared by Schotten–Baumann benzoylation of **1** followed by acetylation.[3]

Benzoylation of Kojic Acid with $SnCl_4$.—Woods' procedure[2] was followed exactly. The solid obtained after NaOH treatment was recrystallized twice from EtOH and yielded 5.9 g of **9**, mp 133–134°, identical with a sample prepared in 84% yield by a brief treatment of **1** with benzoyl chloride in pyridine at −5°.[22] Treatment of 5 g of **9** with HCl as described[2] and recrystallization of the product from EtOH yielded 2.5 g of starting material, mp 131–132°.

Benzoylation of Kojic Acid with CF_3COOH.—Woods' procedure[8] was repeated exactly. After recrystallization from EtOH, **3** was obtained in 27% yield, mp 179–180°. The same

(20) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Interscience, New York, N. Y., 1969, p 1287.
(21) There must be two crystalline forms of **3**. The melting point of the sample obtained here agreed with Woods' values, but it was lowered to 179–180° by further recrystallizations from EtOH.
(22) J. H. Looker, T. T. Okamoto, E. R. Magnson, D. L. Shaneyfelt, and R. J. Prokop, *J. Org. Chem.*, **27**, 4349 (1962).

result was found when the reaction was run with 2 equiv of benzoic acid.

Acetylation of Kojic Acid with H_3PO_4.—Woods' procedure[12] was followed exactly and gave **12** (20% yield after recrystallization from MeOH), mol wt 184 (mass spectrum), mp 135–137° (lit.[1] mp 136–137°), positive $FeCl_3$ test.

Hydrolysis of Acetylkojic Acid (12).—A solution of 200 mg of **12** in 20 ml of H_2O was refluxed for 24 hr. Nmr of the product showed it to be a mixture of **1** (43%) and **12** (57%).

Diacetylkojic Acid (7).—A solution of 2 g of **1** and 2.8 g of AcCl in 50 ml of $CHCl_3$ was refluxed for 8 hr. The product was recrystallized from MeOH to yield **7** in 88% yield, mp 101–102° (lit.[1] mp 102°), negative $FeCl_3$ test.

Acetylation of Kojic Acid with HCl.—Through a refluxing solution of 5 g of **1** in 25 ml of AcOH, HCl was bubbled for 4 hr. After concentration under vacuum, the product was recrystallized from EtOH to yield 4.7 g of **12**, mp 135–136°, identical with the sample prepared above.

Treatment of Kojic Acid with Diethyl Oxalate and CF_3COOH.—Woods' procedure[16] was followed exactly. After recrystallization from EtOH, the starting material was recovered in 26% yield, mp 155–157°.

Treatment of Kojic Acid with Zn and Ac_2O.—The above material (1.6 g) was treated with 2.6 g of Zn dust and 9 ml of Ac_2O.[16] After standing at room temperature for 48 hr and work-up, there was obtained 0.380 g of **7**, mp 102–103°.

Treatment of 5-*O*-Methylkojic Acid (13) with Diethyl Oxalate and Acetylation Reaction.—Woods' procedure[16] was followed using 0.935 g of **13**.[23] After recrystallization from EtOH, the starting material was recovered in 50% yield, mp 162–164°. A portion (0.366 g) was treated with 3 g of Zn dust and 10 ml of Ac_2O at room temperature for 18 hr. After work-up, there was obtained 0.193 g of **14**, mp 124–125°.

Formylation Reactions.—The published procedure[18] was applied to 5 g of **1**, 3 g of **13**, and 1 g of **15** to yield 1.62, 0.95, and 0.61 g of product, respectively. These were found to be unreacted starting materials by nmr and melting point determinations.

$NaBH_4$ Reduction of Kojic Acid.—The published procedure was repeated with 2 g of **1**, substituting $NaBH_4$ for KBH_4. The solid (0.8 g) obtained after work-up and recrystallization from EtOH was identical with the starting material (nmr and melting point).

Registry No.—**1**, 501-30-4; **2**, 33777-41-2; **3**, 33777-42-3; **4**, 25552-08-3; **5**, 644-46-2; **6**, 33777-43-4; **7**, 26209-93-8; **8**, 33777-44-5; **9**, 33886-26-9; **10**, 33777-45-6; **11**, 33777-46-7; **12**, 25552-08-3; **13**, 6269-25-6; **14**, 33777-49-0; **15**, 7559-81-1; **16**, 33777-51-4.

Acknowledgments.—We are grateful to the National Science Foundation for some financial support of this work and J. K. thanks the Department of Organic Chemistry, University of Geneva, for its hospitality (1971–1972).

(23) K. N. Campbell, J. F. Ackerman, and B. K. Campbell, *J. Org. Chem.*, **15**, 221 (1950)

Synthesis of *cis*- and *trans*-3-Chloroazetidinones. II. Direct Acylation of Imines

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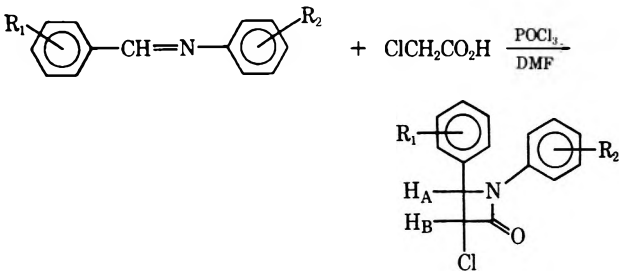
Diaryl-3-halo-2-azetidinones have been prepared by the addition of haloacetic acid and phosphoryl chloride, in dimethylformamide (DMF), to imines,[1] and the authors indicated that single isomers, not mixtures, were obtained. The similarity of the chloroketene reaction with this procedure prompted a more thorough investigation of the haloacetic acid–phosphoryl chloride method.

Examination of the final products from ten reactions (Tables I and II), performed with the haloacetic acid–



phosphoryl chloride conditions,[1] indicated that both cis and trans β-lactams were formed. The coupling constants of vicinal protons in 3-chloro-2-azetidinones, $J(\text{cis}) > J(\text{trans})$, were used to distinguish the isomers.[2]

Since the isomer distribution differed from the original investigation,[1] the reaction was further examined in order to define the disparity. The nearly equal distribution of cis and trans isomers suggested that isomerization may have occurred. No isomerization occurred in refluxing DMF with either *cis*- or *trans*-**1**. However, in the presence of phosphoryl chloride and chloroacetic acid, isomerization was noted. An equilibrium mixture was established within 7 hr, starting from pure *cis*-**1**, and 22 hr from pure *trans*-**1**. This mixture contained 53% *cis*-**1** and 47% *trans*-**1** in both cases. When *cis*-**1** was subjected to these conditions for 2 hr, only 18% *trans*-**1** was formed; however, when *trans*-**1** was refluxed in the reagents for 2 hr, no *cis*-**1** was detected. This small amount of isomerization cannot fully account for the product distribution within the 2-hr reaction time.

Stereochemical evidence was obtained which favored direct acylation of the imine followed by ring closure. Since it is known that acyl chlorides can be formed from carboxylic acids with DMF–phosphoryl chloride,[3] chloroacetyl chloride was added to a solution of benzalaniline in DMF at 80°. The product was **1** (45% cis, 55% trans). No β-lactam was formed at 25°. A ketene mechanism was disfavored since chloroacetyl chloride addition to a DMF solution of benzalaniline and triethylamine at 25° gave only *trans*-**1**. Similar cycloadditions performed in benzene gave only *trans*-**1**.[4]

The proposed intermediate **11** was prepared by the direct acylation of benzalaniline with chloroacetyl chloride. No β-lactam was formed when **11** was stirred in DMF at 25°. However, mixed isomers of **1** (55% cis, 45% trans) were obtained when **11** was added to refluxing DMF. These results compare quite well with the results from the preparative reaction (see Table I). The treatment of **11** with triethylamine in either DMF or benzene at 25° yielded only *trans*-**1**. No β-lactam was observed when **11** was refluxed in benzene. Thus, the possibility of solvent participation, *i.e.*, DMF, cannot be neglected. The zwitterionic intermediate **12**, previously proposed for haloketene

(1) E. Ziegler, T. Wimmer, and H. Mittelbach, *Monatsh. Chem.*, **99**, 2128 (1968).

(2) D. A. Nelson, *Tetrahedron Lett.*, 2543 (1971).

(3) H. H. Bosshard and H. Zollinger, *Helv. Chim. Acta*, **42**, 1659 (1959).

(4) F. Duran and L. Ghosez, *Tetrahedron Lett.*, 245 (1970).

TABLE I

YIELD AND ISOMER DISTRIBUTION OF SOME 3-CHLORO-2-AZETIDINONES

Compd	R_1	R_2	Cis/trans	Mp, °C Cis	Mp, °C Trans	Yield, %
1	H	H	53/47	192[a]	86–87	59
2	*o*-Nitro	H	50/50	*b*	*b*	~1
3	*o*-Nitro	*p*-Methoxy	50/50	148–149	114–116	~1
4	*p*-Nitro	*p*-Methoxy	53/47	134–136	133–134	53
5	*p*-Nitro	H	50/50	170–171	*b*	40
6	*o*-Chloro	H	54/46	*b*	128–130[c]	38
7	*p*-Chloro	*p*-Methoxy	48/52	134–135	97–99	42
8	*p*-Chloro	H	50/50	187–189[a]	102–103	33
9	*o*-Metoxy	H	50/50	106–107	130–131	46
10	*p*-Methoxy	*p*-Methoxy	50/50	162–164	118–119	53

[a] See ref 1. [b] Values could not be obtained for these isomers due to their similar solubility characteristics; ref 5 gave 150–152° for *trans*-5. [c] Value obtained from chloroketene cycloaddition product.[2]

additions,[4] would account for the stereospecificity of the base-catalyzed route (pathway B). Recently, it was proposed that direct acylation (such as **11**), rather than *in situ* prepared ketene, is involved when acyl chloride and imine are present with triethylamine.[5] The lack of stereospecificity for pathway A is not completely understood at this time. See Scheme I.

The extremely low yields of **2** and **3** may be due to reaction of the *o*-nitro groups of their corresponding imines or the intermediates (**13** and **14**). These reactions were very complex (tlc indicated at least 13 components).

SCHEME I

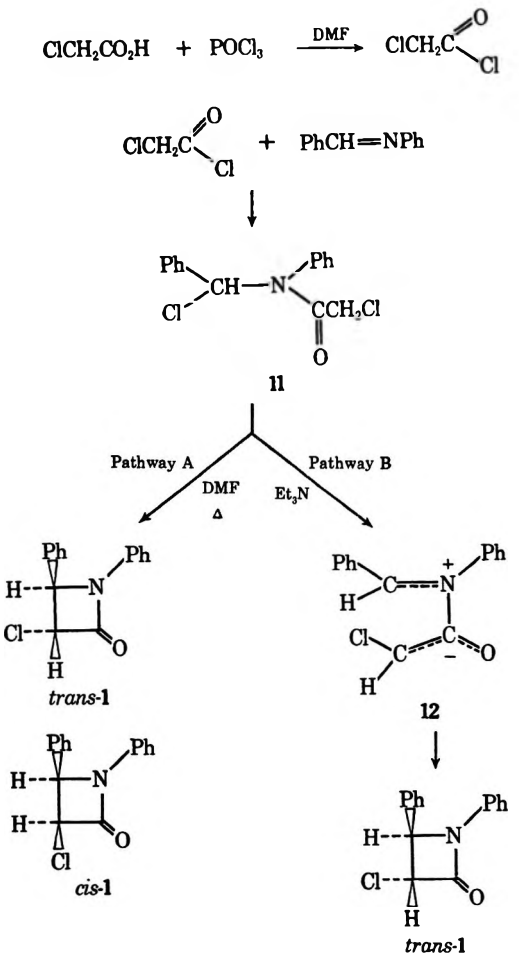
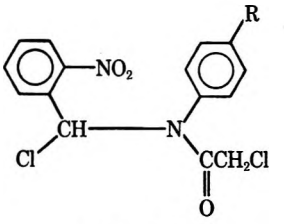


TABLE II

NMR SPECTRAL DATA OF SOME 3-CHLORO-2-AZETIDINONES[a]

	δ_{H_A}, ppm Cis/trans	δ_{H_B}, ppm Cis/trans	J_{AB}, Hz Cis/trans
1	5.42/4.98	5.24/4.58	5.3/2.0
4[b]	5.48/5.13	5.32/4.64	5.5/1.9
5	5.53/5.11	5.34/4.61	5.4/2.0
7	5.35/4.95	5.22/4.57	5.3/1.9
8	5.39/4.99	5.26/4.57	5.4/2.0
9	5.71/5.32	5.25/4.71	5.4/2.0
10	5.32/4.92	5.19/4.57	5.3/1.9

[a] Values are reported relative to internal TMS in $CDCl_3$. [b] See ref 2 for values of **2**, **3**, and **6**.



13, R = OCH_3
14, R = H

When **13** was refluxed in DMF, a complex reaction mixture, containing a trace of **3**, was obtained. Previous investigations[6,7] have shown that cyclization occurred with *o*-nitrophenyl compounds to give substituted isoxazoles.

Experimental Section

Nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60 spectrometer. Chemical shifts are reported as parts per million (δ) relative to tetramethylsilane. Infrared spectra were recorded on a Beckman IR-5 spectrometer. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

All imines used in this study were prepared by direct condensation of the respective benzaldehyde and aniline in ethanol, and were recrystallized. The distilled solvents (Burdick and Jackson Laboratories) were dried: benzene over sodium metal and DMF over molecular sieves type 5A (Linde Co.) followed by elution through an alumina column.

General Preparation of 1,4-Diaryl-3-chloro-2-azetidinones.—To 50 ml of DMF was added 9.1 ml (0.1 mol) of phosphoryl chloride followed by 9.4 g (0.1 mol) of monochloroacetic acid. While this solution stirred, 0.1 mol of imine was added. The solution was heated to reflux for 2 hr (drying tube on condenser), then cooled. The reaction mixture was dissolved in 50 ml of dichloromethane and extracted with 100 ml of water. The

(5) A. K. Bose, G. Spiegelman, and M. S. Manhas, *Tetrahedron Lett.*, 3167 (1971).

(6) I. Tanasescu, C. Anghel, and A. Popescu, *Studia Universitatis Babes-Bolyai, Ser. Chem.*, **9**, 89 (1964).

(7) M. S. Gibson, *Tetrahedron*, **18**, 1377 (1962).

organic layer was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*. The product mixture, oil or crystalline, was analyzed by nmr for isomer distribution. Purification was achieved on an alumina column eluted with dichloromethane or benzene–hexane (2:3 v/v). This solvent was removed, and the isomers were fractionally crystallized with ethanol. In general, the cis isomers were more insoluble in ethanol. Elemental analyses were consistent with the assigned structures. Yields were reported for the combined isolated isomers.

Isomerization of *cis*- and *trans*-1,4-Diphenyl-3-chloro-2-azetidinone (1).—The *cis*- or *trans*-1 (5.0 g, 1.9×10^{-2} mol) was dissolved in 50 ml of DMF. To this was added 1.8 ml (1.9×10^{-2} mol) of phosphoryl chloride and 1.8 g (1.9×10^{-2} mol) of monochloroacetic acid. The solution was stirred at reflux and sampled every 2 hr. The 5-ml samples were dissolved in 10 ml of dichloromethane and extracted with 10 ml of water. The organic layer was evaporated and dissolved in chloroform-d_1 for nmr determination of the isomer distribution. The equilibrium isomer mixture was established within 7 hr from the cis isomer, but 22 hr were required for the trans isomer to reach the 53% cis–47% trans relationship.

2-Chloro-*N*-(α-chlorobenzyl)acetanilide (11).—A benzene solution of 30 g (0.16 mol) of benzalaniline was cooled to 0° with an ice bath. To this was added, dropwise, 18.7 g (0.16 mol) of chloroacetyl chloride over 2 hr while maintaining 0°. Moisture will cause hydrolysis of 11, and chloroacetanilide may precipitate if the reaction is not performed under a dry atmosphere. Recent evidence indicated that adducts such as 11 may be in equilibrium with acyl chloride and imine.[5] The solvent was removed under reduced pressure and a white solid (46.5 g, 96%) was obtained, mp 50–52°. Since the product hydrolyzed readily, it was stored under dry nitrogen. Two characteristic nmr signals (chloroform-d_1) were obtained: nmr δ 3.76 (2 H, s, CH_2Cl), and 7.85 (1 H, s, ClCHN); ir ($CHCl_3$) 1661 cm^{-1} (carbonyl). For comparison, the carbonyl absorbance for chloroacetanilide ($CHCl_3$) was 1681 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}Cl_2NO$: C, 61.2; H, 4.42; N, 4.7. Found: C, 60.7; H, 4.56; N, 5.06.

2-Chloro-*N*-(α-chloro-*o*-nitrobenzyl)-*p*-acetanisidide (13).—The adduct was prepared in a similar manner as 11. Hydrolysis of 13 did not occur as readily as 11. A light yellow solid (92%) was recovered: mp 115–117° dec; nmr (chloroform-d_1) δ 3.81 (2 H, s, CH_2Cl), 3.77 (3 H, s, OCH_3), 8.27 (1 H, s, ClCHN); ir ($CHCl_3$) 1686 (carbonyl), 1533 (asymmetrical nitro), and 1352 cm^{-1} (symmetrical nitro).

Anal. Calcd for $C_{16}H_{14}Cl_2N_2O_4$: C, 52.0; H, 3.79; N, 7.6. Found: C, 52.2; H, 3.97; N, 7.7.

Registry No.—**1b**, 27348-77-2; **3a**, 33281-33-3; **3b**, 33281-34-4; **4a**, 33949-24-5; **4b**, 33276-88-9; **5a**, 33949-26-7; **6b**, 33276-92-5; **7a**, 33949-28-9; **7b**, 33276-93-6; **8b**, 33949-30-3; **9a**, 33949-31-4; **9b**, 33276-96-9; **10a**, 33949-33-6; **10b**, 33276-97-0; **11**, 33949-35-8; **13**, 33949-36-9.

The *A* Value of the Deuterioamino Group Determined by the Nuclear Magnetic Resonance Peak Area Method at −93°

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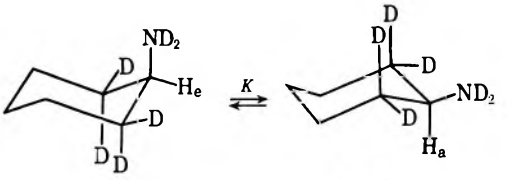
Although there have been many reports concerning the measurement of the axial *vs.* equatorial conformational preference of the hydroxyl group in cyclohexanol,[3] similar data concerning the amino group is relatively scarce, having been derived from indirect kinetic, pK_a, and nuclear magnetic resonance (nmr) techniques which necessarily involve the use of model compounds.[4] There have been no reports concerning the direct measurement of the conformational preference of the amino group in cyclohexylamine itself free from the constraints and possible distortions of locking substituents.[4]

This report concerns the direct measurement of the *A* value[5] (eq 1–2) of the deuterioamino group (ND_2)



(1)

$$A \text{ value} = -\Delta G^\circ = \frac{RT \ln K}{1000} \qquad (2)$$

in cyclohexylamine-*N*,*N*,*2*,*2*,*6*,*6*-d_6 (1) using the low-temperature nmr method. 1 was prepared from cyclohexanol-*2*,*2*,*6*,*6*-d_4 by the method of Streitwieser and Coverdale[6] and was purified by preparative glpc.

Examination of the ^1H nmr spectrum (60 or 100 MHz) of 1 in CD_3OD revealed broadening or coalescence of the various complex $(CH_2)_3$ resonances from about −40 to −70° and subsequent sharpening of the complex $(CH_2)_3$ spectrum at lower temperatures. Likewise, the HCN resonance broadened and sharpened as the temperature was lowered, separating into a large singlet resonance at δ 2.49 (H_a, eq 1) and a much smaller singlet at δ 3.02 (H_e, eq 1). Such spectral behavior is completely consistent with a slowing of the axial ⇄ equatorial equilibration in 1 (eq 1) on the nmr time scale and the direct observation of axial and equatorial conformers. The observed chemical shifts for axial and equatorial HCN protons in 1 are in good agreement with axial (δ 2.50) and equatorial (δ 3.09) HCN chemical shifts in *trans*- and *cis*-4-*tert*-butylcyclohexylamine, respectively (95% ethanol at room temperature).[4a]

Thus, we examined the ^1H nmr spectrum of 1 at −93° in three solvent systems at different concentrations obtaining the axial:equatorial conformer ratio (eq 1) by weighing cut-outs of the HCN proton resonances and by hand planimeter integration. The various equilibrium constants (*K*, eq 1) and associated free energy differences are compiled in Table I. It should be noted that the large equilibrium constants (Table I) at least by nmr standards necessitated the use of relatively high radiofrequency power levels, introducing the possibility of differential saturation effects.[5]

The various *A* values compiled in Table I are in remarkably good agreement with those obtained by more indirect methods.[4] Although the *A* value of ND_2 does

(1) Alfred P. Sloan Research Fellow, 1971–1973.

(2) Supported by Worcester Polytechnic Institute Undergraduate Work-Study Program, Summer 1971.

(3) C. H. Bushweller, J. A. Beach, J. W. O'Neil, and G. U. Rao, *J. Org. Chem.*, **35**, 2086 (1970); E. L. Eliel and E. C. Gilbert, *J. Amer. Chem. Soc.*, **91**, 5487 (1969), and references cited therein.

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(5) For a recent review on the *A* value, see F. R. Jensen and C. H. Bushweller in "Advances in Alicyclic Chemistry," Vol. 3, H. Hart and G. J. Karabatsos, Ed., Academic Press, New York, N. Y., 1971, pp 139–194.

(6) A. Streitwieser, Jr., and C. E. Coverdale, *J. Amer. Chem. Soc.*, **81**, 4275 (1959).

TABLE I

A VALUE OF ND_2 AS A FUNCTION OF CONCENTRATION AND SOLVENT AT −93°

Solvent	Concn, mol/l.	K[a]	A value, kcal/mol
CD_3OD	0.5	34 ± 5	1.3 ± 0.1
	1.0	42 ± 7	1.3 ± 0.1
	1.5	56 ± 9	1.4 ± 0.1
	2.0	55 ± 9	1.4 ± 0.1
50% Pyridine–50% CH_2CHCl (v/v)	2.0	26 ± 4	1.2 ± 0.1
50% CD_2Cl_2–50% toluene-d_8 (v/v)	2.0	55 ± 10	1.4 ± 0.1

[a] According to eq 1; the error assigned to K is the maximum deviation in the measured value.

not change appreciably with concentration in CD_3OD (Table I), K (eq 1) does increase at increasing concentrations of **1**, suggesting an increasing degree of self-association by **1** in preference to complexation by CD_3OD. In those solvents which do not form as strong hydrogen bonds, *e.g.*, 50% pyridine–50% CH_2CHCl (v/v), the equatorial ND_2 conformational preference is reduced slightly in agreement with previous results.[4]

It is then instructive to compare the A value of the amino group to other functionalities having nitrogen bonded to the cyclohexane ring (Table II).[7] Although

TABLE II

PERTINENT A VALUES

Group	A Value, kcal/mol
$-ND_2$	1.2[a]
$-NO_2$	1.1[b]
$-N{=}C{=}N-C_6H_{11}$	1.0[b,c]
$-N{=}C{=}O$	0.51[b]
$-N{=}C{=}S$	0.28[b]
$-N{\equiv}C$	0.21[b]

[a] 2.0 M in 50% pyridine–50% CH_2CHCl at −93°. [b] 2.0 M in CS_2 at −80° except NO_2 at −90°; see ref 7. [c] See ref 8.

unique hybridization of nitrogen in the case of –NCO, –NCS, and $-N{\equiv}C$ apparently leads to more substituent cylindrical symmetry and a relatively low A value,[8] the A value for ND_2 is only slightly larger than that for $-NO_2$ or $-N{=}C{=}N-C_6H_{11}$ (Table II). Indeed, the higher A value for $-ND_2$ as compared to $-NO_2$ may reflect stronger solvent complexation of $-ND_2$ *via* hydrogen bonding and an effectively larger group.

Experimental Section

Nmr spectra were obtained using a Varian Associates HR-60A spectrometer equipped with a custom-built variable temperature probe or using a Varian HA-100 spectrometer equipped with the Varian variable temperature probe and accessories. Temperature measurement was performed using a copper–constantan thermocouple inserted into the sample (HA-100) or permanently in place in the probe (HR-60A) and is accurate to ±0.3° at the sample.

Registry No.—Cyclohexylamine-$N,N,2,2,6,6$-d_6, 33885-12-0.

Acknowledgment.—We are grateful to U. S. Army Natick Laboratories for use of a Varian HA-100 nmr spectrometer.

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Studies on the Syntheses of Heterocyclic Compounds. CDLX.[1] Benzyne Reaction. XIII.[2] Benzyne Reaction of Halogenobenzenes with *N*-Alkylmorpholines

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In previous papers,[3-5] we reported the benzyne reaction of a number of ortho-substituted halogenobenzenes with acetonitrile or phenylacetonitrile in various organic solvents together with the appropriate amines in the presence of sodium amide to give the desired meta-substituted phenylacetonitriles in addition to the meta-substituted amino compounds. During these investigations, when *N*-methylmorpholine was used as solvent in the benzyne reaction of *o*-chloroanisole, 3-methoxy-*N*-methylaniline (**7b**)[3] was obtained as an unusual product in comparatively good yield. Although the formation of Stevens type[6-11] or Sommelet type[12] rearranged products by the reaction of amines with benzyne has been reported, formation of the *N*-alkylaniline derivative by the benzyne reaction of halogenobenzene with N-substituted alicyclic amines has not previously been described, and we have therefore studied several other cases of this reaction.

The benzyne reaction of bromobenzene, *o*-chloroanisole, and *o*-benzyloxychlorobenzene with *N*-methyl-, *N*-ethyl-, *N*-propyl-, *N*-benzylmorpholine, *N*-methylpiperidine, and *N,N'*-dimethylpiperazine was examined and found to give *N*-alkylaniline derivatives. Furthermore, in the case of the benzyne reaction of the halogenobenzenes with *N*-alkylmorpholines, 2-(*N*-alkyl-*N*-phenyl)aminoethanols were obtained in addition to the desired products. All the known products were identified with authentic specimens by comparison of spectroscopic data. The structures of the unknown products were determined by microanalyses and nmr, ir, and mass spectra. These results are shown in Table I. In the benzyne reaction of bromobenzene with *N*-methylmorpholine, when a mixture of bromo-

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(2) Part XII: T. Kametani, S. Shibuya, K. Kigasawa, M. Hiiragi, and O. Kusama, *J. Chem. Soc.*, 2712 (1971).
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(4) T. Kametani, K. Kigasawa, M. Hiiragi, T. Aoyama, and O. Kusama, *J. Med. Chem.*, **14**, 72 (1971).
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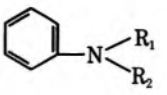
TABLE I

BENZYNE REACTION PRODUCTS OF BROMOBENZENE WITH *N*-ALKYLMORPHOLINE, *N*,*N*′-DIMETHYLPIPERAZINE, AND *N*-METHYLPIPERIDINE[a]



Amine	Compd	R_1	R_2	Yield, %[b]
N-Methylmorpholine	7a	CH_3	H	12.8[c]
	8a	CH_3	CH_2CH_2OH	13.1
N-Methylmorpholine	7a	CH_3	H	13.4[d]
	8a	CH_3	CH_2CH_2OH	13.8
N-Methylmorpholine	7a	CH_3	H	32.8[e]
	8a	CH_3	CH_2CH_2OH	21.6
N-Ethylmorpholine	7c	CH_2CH_3	H	24.4
	8e	CH_2CH_3	CH_2CH_2OH	12.4
N-*n*-Propylmorpholine	7d	$CH_2CH_2CH_3$	H	21.9
	8f	$CH_2CH_2CH_3$	CH_2CH_2OH	3.2
N-Benzylmorpholine	7e	CH_2Ph	H	19.4
	8g	CH_2Ph	CH_2CH_2OH	6.2
	4	CH_2Ph	$CH_2CH_2OCH=CH_2$	12.1
N,*N*′-Dimethylpiperazine	7a	CH_3	H	1.2
	8c	CH_3	$CH_2CH_2NHCH_3$	9.6
	9	$-CH_2CH_2N(CH_3)CH_2CH(CH_3)-$		2.5
N-Methylpiperidine	10	$-(CH_2)_5-$		3.2

[a] All the reactions were carried out under reflux, although *N*-benzylmorpholine was allowed to react at 145–155°. The reaction time was 4 hr in all reactions except that with *N*-methylpiperidine which was 6 hr. [b] Ratio of bromobenzene:amine:$NaNH_2$: (c) 1:2:1.5; (d) 1:2:2; (e) 1:4:4.

benzene, *N*-methylmorpholine, and sodium amide (1:4:4) was used, *N*-methylaniline (**7a**) and 2-(*N*-methyl-*N*-phenyl)aminoethanol (**8a**) were formed in better yield than under other conditions.

In the case of the benzyne reaction of 2-benzyloxychlorobenzene with *N*-methylmorpholine, *N*-methyl-*N*-(2-vinyloxyethyl)aniline (**4a**), and 2-[*N*-methyl-*N*-(3-methylphenyl)]aminoethanol (**8b**) were obtained in addition to the desired product, 3-benzyloxy-*N*-methylaniline (**7f**). Benzyne reaction of bromobenzene with *N*,*N*′-dimethylpiperazine afforded *N*-methyl-*N*-(β-methylaminoethyl)aniline (**8c**) together with **7a** and the Stevens type rearranged product, 2,4-dimethyl-1-phenylpiperazine (**9**). Furthermore, piperidinobenzene was obtained on the benzyne reaction of bromobenzene with *N*-methylpiperidine as reported by Wittig.[6]

The mechanism to explain the formation of these products remained unclear but would involve the reaction of the base with the quaternary salt (**2**) as shown in Scheme I.

Thus, *N*-alkylanilines and *m*-alkoxy-*N*-alkylanilines were obtained by application of the benzyne reaction of bromobenzene and *o*-alkoxyhalogenobenzenes with the appropriate tertiary cyclic amines.

Experimental Section[13]

***N*-Methylaniline (7a) (Benzyne Reaction of Bromobenzene with *N*-Methylmorpholine).**—To a stirred mixture of 25 g of *N*-methylmorpholine and 10 g of sodium amide was added 10 g of bromobenzene under reflux. After the stirring had been continued under reflux for 3 hr, the excess sodium amide was decomposed with saturated ammonium chloride solution under ice cooling. After the addition of water, the mixture was extracted with ether. The organic layer was extracted with 10% HCl. The acidic extract was made basic with 10% NaOH and extracted with ether. The ethereal extract was washed with water, dried over Na_2SO_4, and evaporated. The residual oil was chromatographed on silicic acid using chloroform as an eluent. Evaporation of the first fraction afforded 2.3 g (32.8%) of **7a** as a pale yellowish oil, which was identified by comparison of spectroscopic data with those of the authentic sample. Removal of the second fraction gave 2.07 g (21.6%) of **8a** as a pale yellowish oil, the spectroscopic data of which were identical with those of the authentic specimen:[14] nmr (CCl_4) δ 2.68 (3 H, s, NCH_3), 3.08 (2 H, t NCH_2CH_2OH), 3.38 (2 H, t, NCH_2CH_2OH), 6.10–6.81 (5 H, m, aromatic protons).

3-Methoxy-*N*-methylaniline (7b).—To a stirred mixture of 28 g of *N*-methylmorpholine and 11 g of sodium amide, 10 g of *o*-chloroanisole was added under reflux and the mixture was refluxed with stirring for 4 hr. After the reaction, the mixture was worked up as usual and the crude product was chromatographed on silicic acid using chloroform as an eluent. The first eluent gave 2.1 g (21.9%) of **7b** as a yellow oil, which was identical in ir and nmr spectral comparison with the authentic sample.[3] The second eluent afforded 2.7 g (21.1%) of **8d** as a yellow oil: nmr (CCl_4) δ 2.98 (3 H, s, NCH_3), 3.42 (2 H, t, CH_2CH_2OH), 3.72 (2 H, t, CH_2CH_2OH), 3.78 (3 H, s, OCH_3), 6.02–7.00 (4 H, m, aromatic protons). The oxalate gave colorless needles from ethanol–ether, mp 87–88°. *Anal.* Calcd for $C_{10}H_{15}NO_2 \cdot C_2H_2O_4$: C, 53.13; H, 6.32; N, 5.16. Found: C, 53.28; H, 6.00; N, 5.21.

***N*-Ethylaniline (7c) (Benzyne Reaction of Bromobenzene with *N*-Ethylmorpholine).**—To a stirred mixture of 25 g of *N*-ethylmorpholine and 8.4 g of sodium amide was dropwise added 8.5 g of bromobenzene under reflux. After the stirring had been continued under reflux for 4 hr, the mixture was worked up as usual and the crude product was subjected to silicic acid chromatography. The first chloroform eluent gave 1.6 g (24.4%) of **7c** as a pale yellowish oil, bp 75–80° (15 mm), the hydrochloride of which was recrystallized from ethanol–ether to afford colorless needles, mp 174–177°; this was identical with the authentic specimen by comparison of spctroscopic data and melting point. The second eluent gave 1.1 g (12.4%) of **8e** as a pale yellow oil: nmr (CCl_4) δ 1.12 (3 H, t, CH_2CH_3), 3.41 (2 H, q, CH_2CH_3), 3.43 (2 H, t, CH_2CH_2OH), 3.78 (2 H, t, CH_2CH_2OH), 6.55–7.41 (5 H, m, aromatic protons). The picrate formed yellow prisms from ethanol–ether, mp 103.5–104°. *Anal.* Calcd for for $C_{10}H_{15}NO \cdot C_6H_3N_3O_7$: C, 48.73; H, 4.60; N, 14.21. Found: C, 48.62; H, 4.56; N, 14.05.

***N*-*n*-Propylaniline (7d).**—To a stirred mixture of 2.8 g of *N*-*n*-propylmorpholine and 8.4 g of sodium amide was added 8.5 g

(13) Melting points and boiling points are not corrected; ir and nmr spectra were determined on a Shimazu spectrometer and JNM-MH-60 with tetramethylsilane as internal reference, respectively.

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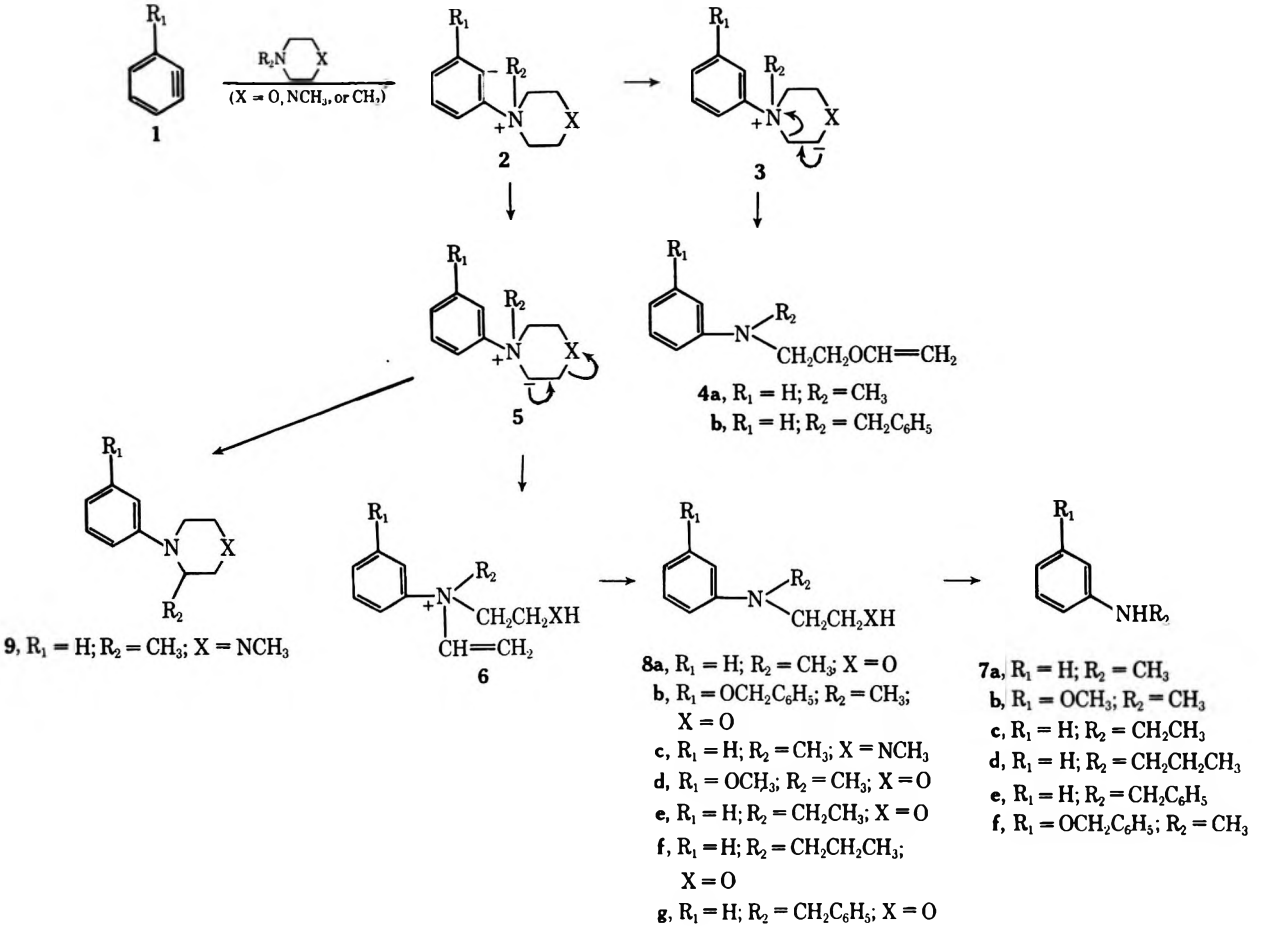
SCHEME I



of bromobenzene under reflux. After the stirring had been contined under reflux for 4 hr, the mixture was worked up as usual to give 1.6 g (21.9%) of **7d** as a pale yellowish oil, from the first chloroform eluent, bp 81–84° (16 mm). the hydrochloride of which was recrystallized from ethanol–ether to afford colorless needles, mp 145–147°; this was identified with the authentic specimen by comparison of spectroscopic data and melting point. The second chloroform eluent afforded 0.3 g (3.2%) of **8f** as a yellow oil: nmr (CCl_4) δ 0.91 (3 H, t, $CH_2CH_2CH_3$), 1.60 (2 H, sextet, $CH_2CH_2CH_3$), 3.31 (2 H, t, $CH_2CH_2CH_3$), 3.46 (2 H, t, CH_2CH_2OH), 3.75 (2 H, t, CH_2CH_2OH), 6.55–7.43 (5 H, m, aromatic protons). This sample was identical with the authentic sample prepared by Wilson's method[14] in ir and nmr spectral comparison.

N-**Benzylaniline** (**7e**).—To a stirred mixture of 18 g of *N*-benzylmorpholine and 4 g of sodium amide was added 4 g of bromobenzene at 145–155°. After the stirring had been continued for 4 hr at the same temperature, the mixture was worked up as usual and the resulting oil was chromatographed on silicic acid using chloroform as an eluent. The first eluent gave 0.9 g (19.4%) of **7e** as a yellow oil, bp 170–190° (7 mm), the hydrochloride of which was recrystallized from ethanol to yield colorless plates, mp 212–214°; this was identical with the authentic specimen by comparison of spectroscopic data.

Evaporation of the second eluate afforded 0.7 g (12.1%) of *N*-benzyl-*N*-(2-vinyloxyethyl)aniline (**4b**) which was recrystallized from ethanol to afford colorless prisms: mp 88–89.5°; nmr (CCl_4) δ 2.05–2.62 (2 H, m, NCH_2–), 3.30–4.02 (4 H, m, $-CH_2OCH{=}CH_2$), 3.85 (2 H, s, NCH_2Ph), 4.48–4.95 (1 H, m, $CH{=}CH_2$), 6.35–7.40 (10 H, m, aromatic protons); mass spectrum *m/e* 253 (M^+). *Anal.* Calcd for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.23; H, 7.20; N, 5.71.

This third eluent gave 0.4 g (6.2%) of **8g** as a yellow oil: ir ν_{max}^{liquid} 3390 cm^{-1} (OH); nmr (CCl_4) δ 3.47 (2 H, t, CH_2CH_2OH), 3.66 (2 H, t, CH_2CH_2OH), 4.53 (2 H, s, CH_2Ph), 6.50–7.41 (10 H, m, aromatic protons).

N-**Methyl-3-benzyloxyaniline** (**7f**).—To a stirred mixture of 16 g of *N*-methylmorpholine and 4.1 g of sodium amide was added dropwise 15.3 g of 2-benzyloxychlorobenzene under reflux. After the stirring had been continued for 4.5 hr under reflux, the mixture was worked up as usual, and the crude product was distilled *in vacuo* to give an oil, bp 170–190° (0.3 mm), which was chromatographed on silicic acid using chloroform as an eluent. Evaporation of the first elution gave 1.6 g (10.8%) of **7f** as a pale yellowish oil: nmr (CCl_4) δ 2.67 (3 H, s, NCH_3), 4.96 (2 H, s, OCH_2Ph), 5.98–7.50 (9 H, m, aromatic protons). The picrate was recrystallized from ethanol to give yellowish prisms, mp 137.5–138.5° (lit.[15] mp 138–138.5°). Removal of the second elution afforded 550 mg (3%) of **8b** as a pale yellowish oil: nmr (CCl_4) δ 2.78 (3 H, s, NCH_3), 3.26 (2 H, t, NCH_2CH_2OH), 3.57 (2 H, t, NCH_2CH_2OH), 4.93 (2 H, s, OCH_2Ph), 6.10–7.45 (9 H, m, aromatic protons). The hydrobromide was recrystallized from isopropyl alcohol–ether to give colorless needles, mp 78–80°. *Anal.* Calcd for $C_{16}H_{19}NO_2 \cdot HBr$: C, 56.81; H, 5.96: N, 4.14. Found: C, 56.55; H, 5.91; N, 4.41.

N-**Phenylpiperidine** (**10**).—To a mixture of 12.5 g of *N*-methylpiperidine and 3.7 g of sodium amide was added 10 g of bromobenzene under reflux. After the stirring had been continued for 6 hr under reflux, the mixture was worked up as usual to give **10**, which was purified as its picrate to give 450 mg (1.9%) of yellow prisms, mp 144–145° (lit.[16] mp 145–146°).

Benzyne Reaction of Bromobenzene with *N*,*N*′-**Dimethylpiperazine**.—To a stirred mixture of 20 g of *N*,*N*′-dimethylpiperazine and 10 g of sodium amide was added 10 g of bromobenzene under reflux. After the stirring had been continued for 4 hr under reflux, the mixture was worked up as usual and the crude product was chromatographed on silicic acid. Removal of the elution with chloroform afforded 80 mg (1.2%) of **7a**, the spectroscopic data of which were identical with those of the authentic specimen. Evaporation of the successive elution with 5% ethanol–chloroform gave 300 mg (2.5%) of 2,4-dimethyl-1-phenylpiperazine (**9**): nmr (CCl_4) δ 1.08 (3 H, d, $CHCH_3$), 2.01–2.95 [4 H, m, $-CH_2N(CH_3)CH_2-$], 2.30 (3 H, s, NCH_3),

(15) A. A. Morton and W. R. Salunwhite, Jr., *J. Biol. Chem.*, **179**, 259 (1949); *Chem. Abstr.*, **44**, 2511 (1950).

(16) C. H. Horning and F. W. Bergstrom, *J. Amer. Chem. Soc.*, **67**, 2110 (1945).

2.98–3.31 (2 H, m, CH_2NPh), 3.52–4.00 (1 H, m, $CHCH_3$), 6.55–7.35 (5 H, m, aromatic protons). The hydrochloride was recrystallized from ethanol–ether to give a colorless powder, mp 208–212° dec. *Anal.* Calcd for $C_{12}H_{18}N_2 \cdot 2HCl$: C, 54.76; H, 7.66; N, 10.64. Found: C, 54.53; H, 7.88; N, 10.47.

Finally, the elution with 10% ethanol–chloroform was evaporated to leave 1.1 g (9.7%) of *N*-metahyl-*N*-(2-methylaminoethyl)aniline (**8c**): nmr (CCl_4) δ 2.45 (3 H, s, $NHCH_3$), 2.78 (2 H, t, CH_2NHCH_3), 2.98 (3 H, s, $PhNCH_3$), 3.44 (2 H, t, $PhNCH_2$), 6.45–7.3 (5 H, m, aromatic protons). The hydrochloride was recrystallized from ethanol–ether to give pale yellowish needles, mp 159–160°. *Anal.* Calcd for $C_{10}H_{16}N_2 \cdot HCl$: C, 59.84; H, 8.54; N, 13.96. Found: C, 59.69; H, 8.69; N, 13.74.

The Reaction of 2-(*N*-Methyl-*N*-phenyl)aminoethanol (8a) with Sodium Amide.—A mixture of 1.5 g of **8a** and 0.78 g of sodium amide was stirred for 4 hr at 150–160° in the presence of 2.4 g of *N*-methylmorpholine as solvent. After cooling, the excess sodium amide was decomposed with saturated ammonium chloride solution under ice cooling and extracted with ether. The extract was washed with water, dried over Na_2SO_4, and evaporated. The residual oil was chromatographed on silicic acid using chloroform as an eluent. Evaporation of the solvent afforded 45 mg (4.2%) of **7a**, the spectroscopic data of which were identical with those of the authentic specimen.

Registry No.—**4b**, 33905-37-2; **7f**, 33905-38-3; **8b**, 33905-39-4; **8b** HBr, 33905-40-7; **8c**, 2412-49-9; **8c** HCl, 33905-42-9; **8d**, 33905-43-0; **8d** oxalate, 33905-44-1; **8e**, 92-50-2; **8e** picrate, 33905-46-3; **8g**, 33905-47-4; **9**, 33905-48-5; **9** HCl, 33905-49-6; bromobenzene, 108-86-1; *o*-chloroanisole, 766-51-8; *o*-benzyloxychlorobenzene, 949-38-2; *N*-methylmorpholine, 109-02-4; *N*-ethylmorpholine, 100-74-3; *N*-propylmorpholine, 23949-50-0; *N*-benzylmorpholine, 10316-00-4; *N*-methylpiperidine, 626-67-5; *N,N'*-dimethylpiperazine, 106-58-1.

Acknowledgments.—We thank President A. Yanagisawa and Director O. Takagi of the Grelan Pharmaceutical Co., Ltd., for their encouragement. We also thank Dr. K. Fukumoto and Dr. S. Shibuya, Pharmaceutical Institute, Tohoku University, for their kind suggestions.

A Bisulfite Mediated Oxidation of Thebaine. Formation of 6-*O*-Demethylsalutaridine[1]

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A method for removal of ketonic compounds from thebaine and other nonketonic alkaloids involves treatment of such a mixture with an aqueous sodium bisulfite solution.[2] Water-soluble bisulfite addition products are readily separated from the thebaine by simple extraction. We have noted, however, that in certain instances the yields of recovered thebaine (**1**) were unexpectedly low. Further study indicated that thebaine was consumed under the extraction conditions only when the process was carried out in the presence of oxygen.

Thus, by reaction with aqueous sodium bisulfite (pH 4) and oxygen, thebaine (**1**) is oxidized to 6-*O*-demethylsalutaridine ($\Delta^{8(14)}$-7-oxothebainone) (**7**). The identity of the product was established by direct comparison with material obtained by the action of alkali on 14-bromocodeinone.[3,4] Thebaine is unaffected by a sodium phosphate buffer, pH 4, in the presence of oxygen, or sodium bisulfite buffer, pH 4, in the absence of oxygen. Furthermore, when oxygen is excluded, thebaine is unaffected by a bisulfite solution which has been previously shaken for 2 hr in the presence of oxygen. The possibility that the production of **7** is dependent on the alkaline treatment in the isolation procedure was eliminated, since, on omitting this process, **7** was produced in undiminished yield.

To determine the origin of the oxygen functions, ^{18}O tracer techniques were applied. An initial series of experiments was conducted to determine the extent of exchange of the carbonyl functions with water. The product **7** was subjected to the conditions under which it was formed except that the bisulfite solution used was prepared with ^{18}O-enriched water. Mass spectrometric analysis[5] of the reisolated product indicated that exchange at both carbonyls had occurred to the extent of about 10% after 1 hr, 40% after 3 hr, and 95% after 24 hr. Therefore, isotopic studies became definitive if the reaction time was reduced to 1 hr, a process which was feasible since the product **7** was still isolated in sufficient yield (15%).

The possibility that either water or molecular oxygen was the source of the oxygen functionalities in **7** was explored by conducting the oxidation reaction first with ^{18}O-enriched water and then with ^{18}O-enriched O_2. Mass spectrometric analysis indicated that the ^{18}O enrichment of the product obtained from the first experiment was due only to exchange of the carbonyl oxygen atoms with the $H_2{}^{18}O$. The product obtained from the reaction in an $^{18}O_2$ atmosphere showed no ^{18}O enrichment.

The remaining possible source of the oxygen which is incorporated into 6-*O*-demethylsalutaridine is bisulfite. Since it was previously established that water is not incorporated into the product, testing the bisulfite hypothesis was somewhat simplified. Thus, to prepare ^{18}O-labeled bisulfite a 1 *N* sodium bisulfite solution was prepared using ^{18}O-enriched water, and it was stirred under nitrogen for 28 hr. Thebaine was then added to this solution and allowed to react as usual. Analysis of the product indicated a 100% isotopic enrichment of one oxygen atom. The initial bisulfite $H_2{}^{18}O$ exchange period was then increased to 48 hr and subsequent oxidation of thebaine in this solution produced a product which was again 100% isotopically enriched for one oxygen atom. The fact that the same enrichment was obtained with solutions in which exchange was allowed to occur for different periods establishes that the $HSO_3^- - H_2{}^{18}O$ exchange was complete within 28 hr. Furthermore, it eliminates the possibility that the result obtained with the 28-hr exchange solution could have been due to a 50% isotopic enrichment of both carbonyl oxygens in the product.

(1) Supported in part by Grant MH 12797 from the National Institute of Mental Health, U. S. Public Health Service.

(2) H. Rapoport, C. H. Lovell, H. R. Reist, and M. E. Warren, Jr., *J. Amer. Chem. Soc.*, **89**, 1942 (1967).

(3) W. Fleischhacker, F. Vieböck, and F. Zeidler, *Monatsh. Chem.*, **101**, 1215 (1970).

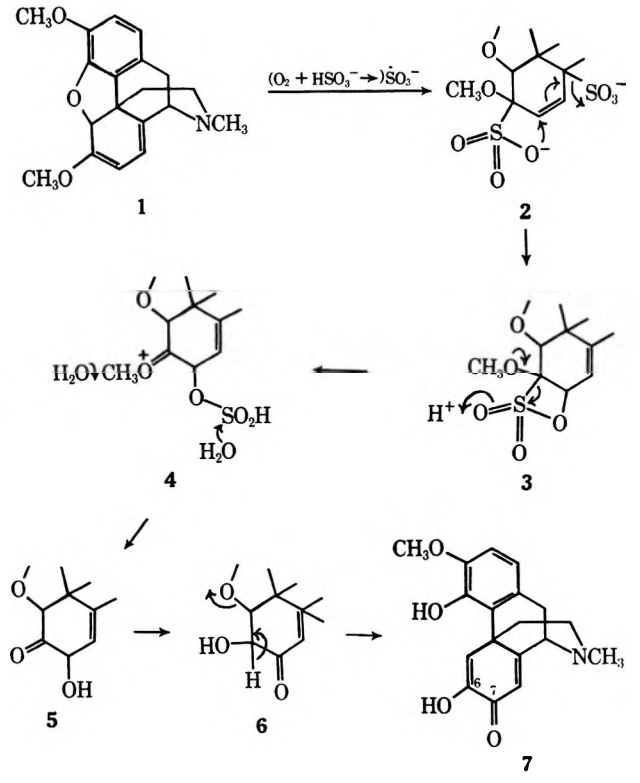
(4) D. E. Rearick and M. Gates, *Tetrahedron Lett.*, 507 (1970).

(5) C. D. Snyder and H. Rapoport, *Biochemistry*, **7**, 2318 (1968); **9**, 2033 (1970).

For mechanistic considerations, since only one oxygen atom is incorporated, it is reasonable to assume that it is the oxygen atom at C-7 of **7** which is incorporated from bisulfite. Any mechanism proposed for this transformation must be consistent with the following observations: (a) thebaine is unaffected by a bisulfite solution in the absence of O_2; (b) molecular oxygen must be present during the course of the reaction in order for the conversion to occur; and (c) the source of the oxygen atom which is incorporated into the product is bisulfite.

These conditions have been incorporated in the mechanism proposed in Scheme I. The postulated first

SCHEME I



step is the 1,4 addition of two bisulfite radical ions to form the disulfonate **2**. The radical ions in turn are proposed as formed by the action of oxygen on aqueous bisulfite, conditions which are well documented to convert olefins to sulfonates and disulfonates[6] *via* radical intermediates. Reaction then proceeds *via* displacement of the sulfonate at position 14 to form the β-sultone **3**. The latter then collapses to **4** which is hydrolyzed to the α-hydroxy ketone **5**. Tautomeric rearrangement to **6** is followed by β elimination to form the morphinandienone, 6-*O*-demethylsalutaridine (**7**). Clearly, alternatives exist for the route from β-sultone **3** to dienone **7** involving essentially the same principles.

Experimental Section

6-*O*-Demethylsalutaridine (7).—A solution of 9 g of thebaine (**1**) in 250 ml of 1 *N* sodium bisulfite was shaken for 3 hr under an atmosphere of oxygen. The solution was then brought to pH 11 with 30% aqueous sodium hydroxide and extracted with two 75-ml portions of benzene–hexane, 1:1. After drying (Na_2SO_4) and removal of the solvent, the first extract produced 0.67 g of a 2:1 mixture of thebaine and **7** and the second extract produced 0.14 g of a 3:2 mixture of the thebaine and **7**. The aqueous phase was adjusted to pH 8.0 with concentrated HCl and extracted with methylene chloride (four 75-ml portions). The extracts were combined and dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield **7**, 5.10 g (64%) based on thebaine consumed, as a white solid after crystallization from benzene, mp 184–186° turning red-brown, identical with material prepared by the action of alkali on 14-bromocodeinone.[3,4]

Isotopic Experiments. A. ^{18}O Determinations.—Reactions were carried out for 1 hr in the presence of $H_2{}^{18}O$, $^{18}O_2$, or $NaHS^{18}O_3$, and the purified product was examined for ^{18}O by nonoxidative pyrolysis as previously described.[5] The ^{18}O content of the carbon monoxide produced was determined by mass spectrometry. Pyrolysis of an equal amount of unlabeled product provided a natural abundance background determination. The ^{18}O content of the $H_2{}^{18}O$ and O_2 used are 2.0 and 1.6%, respectively. All isotope assays were performed using a Consolidated Electrodynamics Corp. Model 130 mass spectrometer.

B. Apparatus.—The oxidations were conducted in an apparatus[7] which is commonly used for hydrogenation at atmospheric pressure, fitted for the introduction of oxygen instead of hydrogen. All experiments using isotopically enriched materials were conducted with this apparatus.

Registry No.—**7**, 27669-33-6.

(6) E. E. Gilbert, "Sulfonation and Related Reactions," Interscience, New York, N. Y., 1965, p 150.

(7) K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill, New York, N. Y., 1960, p 228.

A Novel Intramolecular Rearrangement of a 1,4 Dipole

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While cycloaddition reactions of 1,4 dipoles are well documented,[1,2] intramolecular rearrangements of these dipoles have rarely been observed.[1] We wish to report experimental evidence for a unique 1,4-dipolar intramolecular rearrangement resulting from the reaction of 4-phenyl-1,2,4-triazoline-3,5-dione[3] (**1**) with vinyl esters.

Equimolar quantities of **1** and vinyl acetate (**2**) react in methylene chloride at 60° yielding 1-formyl-2-acetyl-4-phenyl-1,2,4-triazoline-3,5-dione (**3**) exclusively. Isopropenyl acetate (**4**) reacts in a similar manner to give 1-acetylmethyl-2-acetyl-4-phenyl-1,2,4-triazoline-3,5-dione (**5**).

A plausible mechanism for these reactions would involve the unusually stable 1,4 dipole[4] (**6**) as the reactive intermediate, formed *via* initial reaction of the electron-poor nitrogen double bond with the electron-rich double bond of the vinyl ester. The 1,4 dipole, once formed, could undergo an intramolecular nucleophilic attack by nitrogen on the carbonyl carbon displacing the ester oxygen (path a, Scheme I). Intramolecular nucleophilic attack by nitrogen is sterically hindered by large R_2 groups, decreasing the relative yield of the product

(1) R. Huisgen, *Z. Chem.*, **8**, 290 (1968).

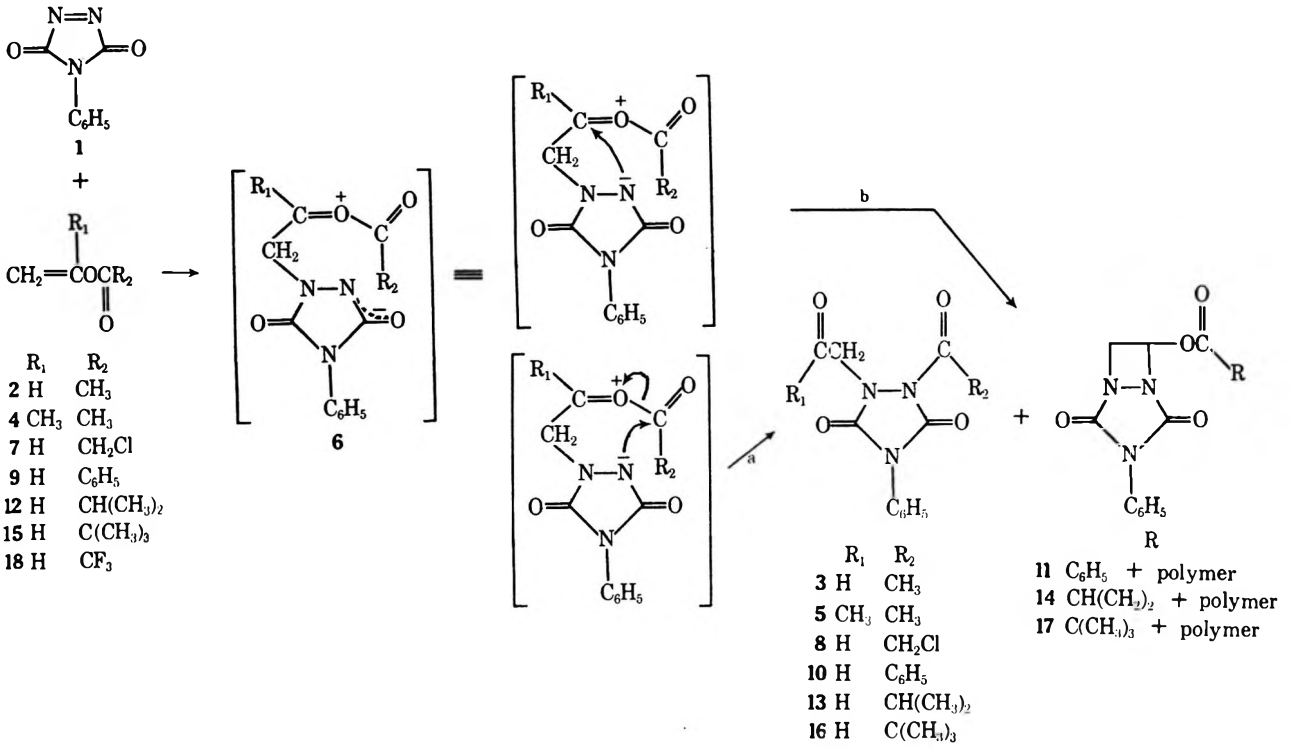
(2) E. K. Von Gustorf, D. V. White, B. Kim, K. Hess, and J. Leitich, *J. Org. Chem.*, **35**, 1155 (1970).

(3) J. C. Stickler and W. H. Pirkle, *ibid.*, **31**, 3444 (1966).

(4) 1,4 dipoles of a similar nature have previously been reported.[5]

(5) (a) Ref 2; (b) S. R. Turner, L. J. Guilbault, and G. B. Butler, *J. Org. Chem.*, **36**, 2838 (1971).

SCHEME I[a]



[a] Structural assignments for 11 are tentative only. See Experimental Section.

resulting from rearrangement (Table I); thus, while the 1,4 dipoles formed in the reactions of 2, 4, and vinyl chloroacetate (7)[6] rearrange exclusively, the dipoles of vinyl isobutyrate (12), vinyl pivalate (15), and vinyl benzoate (9)[6] form two other products as well, 1,3,5-triazabicyclo[3.2.0]hepta-2,4-diones *via* path b, Scheme I, and polymers by a mechanism previously described.[7]

A third mechanistic possibility—reaction through an acylium ion—can be eliminated on the basis of two reactions listed in Table I. A highly unstable chloro-

TABLE I

RELATIVE YIELDS OF PRODUCTS

Ester	Yield of trisubstituted triazoline-diones, %	Yield of 1,3,5-triazabi-cyclo[3.2.0]-hepta-2,4-diones, %	Yield of polymer, %
2, 4, 7	100	0	0
12	77	8	15
15	42	42	16
9	6	7	87

acylium ion would be required as the reactive intermediate in the reaction of 7 with 1. Also, 9 reacts with 1 to give polymeric material as the major product, contrary to what would be expected (*i.e.*, a high yield of 10) if a benzacylium ion were the reactive intermediate.

The apparent differences in reactivities of other vinyl esters offer further evidence for a 1,4-dipolar intermediate. Electron-donating groups located close to the positive center stabilize the dipole, while electron-withdrawing groups have an opposite effect. Thus, in comparison to the vinyl acetate reaction, which required 4 hr for completion,[8] the characteristic red color of 1 disappeared twice as fast in reaction with 4, ten times slower in reaction with 7, and vinyl trifluoroacetate (18) failed to react after 96 hr.

(6) Electronic effects may also influence the relative yields of products in the vinyl chloroacetate and vinyl benzoate reactions.

(7) The polymers obtained in these reactions are related to those reported earlier: S. R. Turner, L. J. Guilbault, and G. B. Butler, *Polym. Lett.*, **9** (2), 115 (1971).

Experimental Section[9]

General Procedure.—To a solution of 0.500 g (2.86×10^{-3} mol) of 1 in 25 ml of reagent grade methylene chloride (dried over 4-Å molecular sieves) was added 2.86×10^{-3} mol of the vinyl ester. The intense red solution was transferred to a thick-walled glass tube, which was sealed under vacuum following two freeze–thaw cycles in liquid nitrogen. The tube was placed in a 60° constant-temperature bath and removed after color discharge to light yellow was noted. The tube was then opened and the contents were poured through a coarse sintered glass funnel into 250 ml of stirred hexane in order to precipitate any polymer formed. Polymer, if formed, was filtered and the filtrate was evaporated on a rotary evaporator, leaving nonpolymeric products behind. The nonpolymeric products were separated and purified as described below, and dried at 58° (0.03 mm) overnight before microanalysis. All nonpolymeric products were odorless, white, crystalline solids; the polymeric products were odorless, white, amorphous solids. Nmr data may be found in Table II.

1-Formyl-2-acetyl-4-phenyl-1,2,4-triazoline-3,5-dione (3) was recrystallized twice from a methylene chloride–hexane solvent pair: yield 0.56 g (75%); mp 130–131°; ir (KBr) 2860 (w), 2750 (w), 1800 (m), 1730 cm^{-1} (s, b).

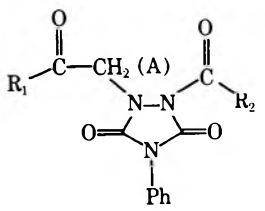
Anal. Calcd for $C_{12}H_{11}N_3O_4$: C, 55.20; H, 4.20; H, 16.09. Found: C, 55.34; H, 4.28; N, 15.95.

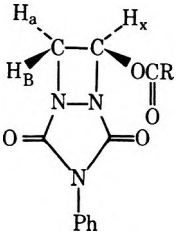
1-Acetylmethyl-2-acetyl-4-phenyl-1,2,4-triazoline-3,5-dione (5) was recrystallized twice from a methylene chloride–hexane solvent pair: yield 0.63 g (80%); mp 107–108°; ir (KBr) 1800 (m), 1750 (s), 1730 (s) 1720 cm^{-1} (s).

(8) The time required for complete disappearance of the characteristic red color of 1, using 2.86×10^{-3} mol of reactants in all reactions.

(9) Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Ir spectra were taken on a Beckman IR-8 spectrophotometer and nmr spectra on a Varian A-60A spectrometer. Mass spectral data were obtained using a Hitachi Perkin-Elmer RMU mass spectrometer and resulted in the molecular ion and reasonable cracking patterns for all products having analytical data. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Ga.

TABLE II
NMR DATA[a]





Compd	R_1	R_2	A	Compd	R	H_a	H_b	H_x	J_{AB}	J_{AX}	J_{BX}
3	9.56 (s, 1)	2.60 (s, 3)	4.80 (s, 2)	11	b	4.20[c] (m)		6.19 (m)			
5	2.10 (s, 3)	2.52 (s, 3)	4.78 (s, 2)	14	2.64 (d, 6)	4.58 (q, 1)	4.29 (q, 1)	6.56 (q, 1)	10	6	5
8	9.60 (s, 1)	4.97 (s, 2)	4.72 (s, 2)		2.23 (d, 6)						
10	9.66 (s)	b	4.78 (s)	17	1.20 (s, 9)	4.60 (q, 1)	4.27 (q, 1)	6.49 (q, 1)	10	6	5
13	9.57 (s, 1)	4.15 (m, 1)	4.79 (s, 2)								
		1.25 (d, 6)									
16	9.53 (s, 1)	1.37 (s, 9)	4.63 (s, 2)								

[a] In chloroform-d_1 with 1% TMS as internal standard. Values reported in δ units. *N*-Phenyl protons appeared in the δ 7.41–7.50 region for all compounds. Abbreviations used are s, singlet; d, doublet; q, quartet; m, multiplet. [b] Complex multiplet absorption in the δ 7.2–7.8 region was observed for the two phenyl groups. [c] Complex absorption pattern for both protons.

Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.73; H, 4.76; N, 15.27. Found: C, 56.83; H, 4.80; N, 15.33.

1-Formylmethyl-2-chloroacetyl-4-phenyl-1,2,4-triazoline-3,5-dione (**8**) precipitated upon pouring the reaction mixture into 250 ml of stirred hexane. Nmr spectra of the crude material indicated no polymer formation. Purification was effected by twice recrystallizing the crude product from hexane–methylene chloride: yield 0.80 g (95%); mp 157–158°; ir (KBr) 2880 (w), 2745 (w), 1810 (s), 1760–1710 cm^{-1} (s, b).

Anal. Calcd for $C_{12}H_{10}ClN_3O_4$: C, 48.91; H, 3.42; N, 14.26. Found: C, 49.00; H, 3.58; N, 14.20.

Separation of **1-formylmethyl-2-benzoyloxy-4-phenyl-1,2,4-triazoline-3,5-dione** (**10**) and **3-phenyl-6-benzoyloxy-1,3,5-triazabicyclo[3.2.0]hepta-2,4-dione** (**11**) has not yet been achieved, and their structural assignments have been tentatively made based on the nmr spectrum of the mixture, total yield 0.11 g (13%).

1-Formylmethyl-2-(2-methylpropionyl)-4-phenyl-1,2,4-triazoline-3,5-dione (**13**) and **3-phenyl-6-(2-methylpropionyloxy)-1,3,5-triazabicyclo[3.2.0]hepta-2,4-dione** (**14**) appeared as an oil after evaporation of the solvent. The mixture was dissolved in the minimum amount of methylene chloride necessary to attain solution followed by addition of the minimum amount of hexane necessary to cause slight cloudiness. The solution was allowed to stand at room temperature for 2–3 days, resulting in fractional crystallization (**14** precipitated first) of the solids. The procedure was repeated several times in order to obtain pure samples of each product.

Data for **13** follow: yield 0.50 g (60%); mp 100–101°; ir (KBr) 2870 (w), 2750 (w), 1800 (m), 1735 (s, b), 1720 cm^{-1} (s, shoulder).

Anal. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53. Found: C, 58.29; H, 5.36; N, 14.45.

Data for **14** follow: yield 0.50 g (6.3%); mp 163–164°; ir (KBr) 1780 (m), 1755 (s), 1720 cm^{-1} (s).

Anal. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53. Found: C, 58.00; H, 5.31; N, 14.36.

1-Formylmethyl-2-(2,2′-dimethylpropionyl)-4-phenyl-1,2,4-triazoline-3,5-dione (**16**) and **3-phenyl-6-(2,2′-dimethylpropionyl)-1,3,5-triazabicylo[3.2.0]hepta-2,4 dione** (**17**) were purified using the same procedure employed for **13** and **14**, substituting hexane–ether as the solvent pair.

Data for **16** follow: yield 0.31 g (36%); mp 135–136°; ir (KBr) 2880 (w), 2740 (w), 1780 (m), 1740 (s), 1720 (s), 1700 cm^{-1} (s).

Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.30; H, 5.79; N, 13.69.

Data for **17** follow: yield 0.30 g (36%); mp 171–172°; ir (KBr) 1780 (m), 1750 (s), 1725 cm^{-1} (s).

Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.18; H, 5.70; N, 13.89.

Vinyl trifluoroacetate (**18**) was allowed to stand with **1** for 96 hr at 60°. Approximately 80% of **1** was recovered unreacted along with 10% of a tan solid, which appeared to be an oligomeric decompositon product of **1**.

Registry No.—**3**, 33981-32-7; **5**, 34050-55-0; **8**, 33981-33-8; **10**, 34050-56-1; **11**, 33981-34-9; **13**, 33981-35-0; **14**, 33981-36-1; **16**, 34050-57-2; **17**, 33981-37-2.

Acknowledgment.—We gratefully acknowledge the partial support of this work by the Tennessee Eastman Company in the form of a fellowship grant to S. R. T.

Intramolecular Catalysis in the Aminolysis of Thiol Esters

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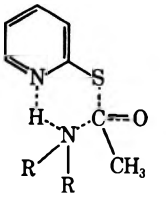
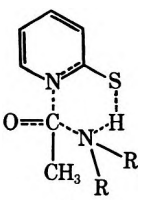
Received October 5, 1971

Although the aminolysis of esters has received considerable study, only one example of intramolecular amine-catalyzed aminolysis in water has been reported.[3] We report here the first example of intramolecular amine-catalyzed aminolysis of a thiol ester in water. 2-Pyridyl thiolacetate (**1a**) was chosen as the thiol ester



1a



1b

because the pyridyl nitrogen is in a favorable geometric position to act as a general base and because thiol esters of 2-thiopyridone have an unusually high reactivity in

(1) Postdoctoral Fellow of the National Institutes of Health, 1969–present.

(2) To whom inquiries should be addressed.

(3) (a) T. C. Bruice and S. M. Felton, *J. Amer. Chem. Soc.*, **91**, 2799 (1969); (b) S. M. Felton and T. C. Bruice, *ibid.*, **91**, 6721 (1969).

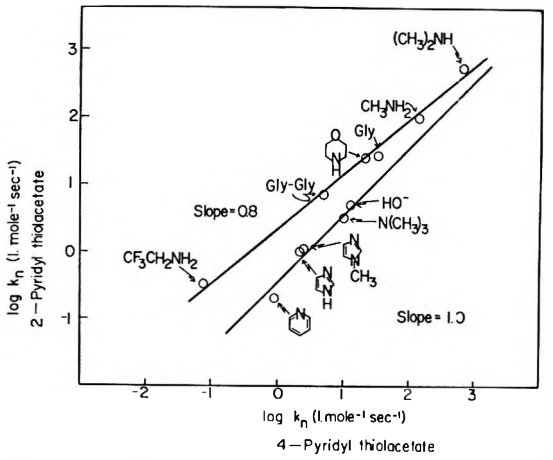


Figure 1.—A plot of the log of the second-order rate constants (k_n) for the reaction of bases with 2-pyridyl thiolacetate *vs.* the same function for 4-pyridyl thiolacetate.

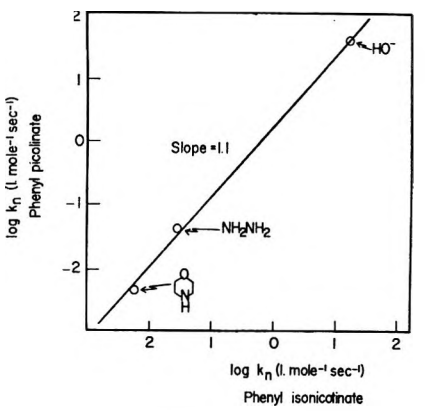


Figure 2.—A plot of the log of the second-order rate constant (k_n) for the reaction of bases with phenyl picolinate *vs.* phenyl isonicotinate. The data for hydroxide ion and hydrazines are from ref 3b.

peptide synthesis.[4] The second-order rate constants (k[B][E]) for the reaction of hydroxide ion and a series of primary, secondary, and tertiary amines with **1a** and 4-pyridyl thiolacetate (**1b**) were obtained. Log k_n for the reaction of **1a** is plotted *vs.* log k_n for **1b** in Figure 1. This plotting technique is a means of comparing nucleophilicities which normalizes scattering of points due to steric effects, electronic effects, etc.[5] In this case it compares the nucleophilicity of a series of nucleophiles toward **1a** and **1b**. **1b** was chosen for comparison because it is structurally similar to **1a** but the pyridyl nitrogen is too distant from the reaction site to be involved in catalysis. Inspection of Figure 1 reveals that the nucleophiles fall on two distinct lines. Hydroxide ion and the tertiary amines fit a line of slope 1, while the primary and secondary amines fit a line of slope 0.8. The slopes in plots of this nature are related to the Brønsted β coefficient; *i.e.*, a slope of 1.0 indicates that the β is the same for both esters and a slope different from 1 indicates that the β values are different for the two esters. Thus, the plot shown in Figure 1 indicates that the mechanism associated with the tertiary amines and hydroxide ion is the same for both thiol esters, while the mechanisms of the reaction of the primary and secondary amines appear different for each thiol ester. The reaction of hydroxide ion and the tertiary amines with both thiol esters must proceed *via* nucleophilic attack at the carbonyl group. **1b** reacts with the primary and secondary amines by the same mechanism as the tertiary amines, while the reactivity of the primary and secondary amines is enhanced over the tertiary amines for **1a**. This enhanced reactivity of amines containing dissociable protons can be attributed to intramolecular general base assistance. The intramolecular general base mechanism could involve the pyridyl nitrogen with a transition state as pictured in **1a** or it could involve the sulfur after a rapid *S*- to *N*-acyl shift with a transition state as shown in **1b**. The mechanism involving sulfur as a general base is ruled out because the basicity of the sulfur is extremely low,[6] negating its role as a general base catalyst. Thus the preferred mechanism for the intramolecular general base catalyzed reaction of the primary and secondary amines with **1a** is the one involving proton removal by the pyridyl nitrogen.

Phenyl picolinate (**2a**) was examined by this same plotting technique in an attempt to find a further example of intramolecular amine-catalyzed aminolysis of an ester in water. The logarithms of the second-order rate constants for the reaction of **2a** and phenyl isonicotinate (**2b**) with a primary amine, a secondary amine, and hydroxide are plotted in Figure 2. Figure 2 shows that all points lie on a line of slope 1.1. This indicates that the amines react *via* the same mechanism as hydroxide ion with both esters. Since hydroxide ion cannot react *via* an intramolecular mechanism, it follows that the reaction of the amines with **2a** is not proceeding *via* an intramolecular amine-catalyzed mechanism. Thus, Bruice and Felton's previous suggestion[3b] that the pyridyl nitrogen cannot get close enough to the incoming amine to remove a proton is probably correct.

Experimental Section

Materials.—The amines or their hydrochlorides were purified as described elsewhere.[3b] 2-Pyridyl thiolacetate. (**1a**),[7] phenyl picolinate (**2b**),[3b] and phenyl isonicotinate (IIb)[3b] were prepared according to literature procedures.

4-Pyridinium Thiolacetate Hydrochloride.—To 5.56 g (0.05 mol) of 4-mercaptopyridine dissolved in 600 ml of acetone a slight molar excess of acetyl chloride was added. After several minutes yellow crystals formed. The reaction mixture was allowed to stand at room temperature for 30 min and then the yellow crystals were filtered off and recrystallized from acetonitrile: melting point could not be determined because the salt decomposed on heating; ir (KBr) 1710 (C=O). Calcd for C_7H_8NOSCl: C, 44.32; H, 4.26; S, 16.90. Found: C, 44.16; H, 4.06; S, 16.76.

Kinetics.—Reaction rates were determined spectrophotometrically in water at 30° by a previously published procedure.[3b] The ionic strength was maintained at 1 *M* by adding KCl. The change in absorbance was followed at 324, 342, 290, and 240 nm for **1a**, **1b**, **2a**, and **2b**, respectively.

Registry No.—4-Pyridinium thiolacetate hydrochloride, 34224-19-6.

Acknowledgment.—This research was supported from a grant from the National Institutes of Health.

(4) K. Lloyd and G. T. Young, *Chem. Commun.*, 1400 (1968).

(5) M. J. Gregor and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 2121 (1967).

(6) R. A. Jones and A. R. Katritzky [*J. Chem. Soc.*, 3610 (1958)] report the pK_a of 2-thiopyridone to be −1.38.

(7) H. Kato, K. Tanaka, and M. Ohta, *Bull. Chem. Soc. Jap.*, **39**, 1248 (1966).

The Chemiluminescence of Tetrachloroethylene Carbonate and Related Compounds

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Received September 13, 1971

We wish to report the new chemiluminescent reaction[1] of tetrachloroethylene carbonate (**1b**) with hydrogen peroxide in the presence of a fluorescer. As shown in expt 1 of Table I, a quantum efficiency of 0.98% was

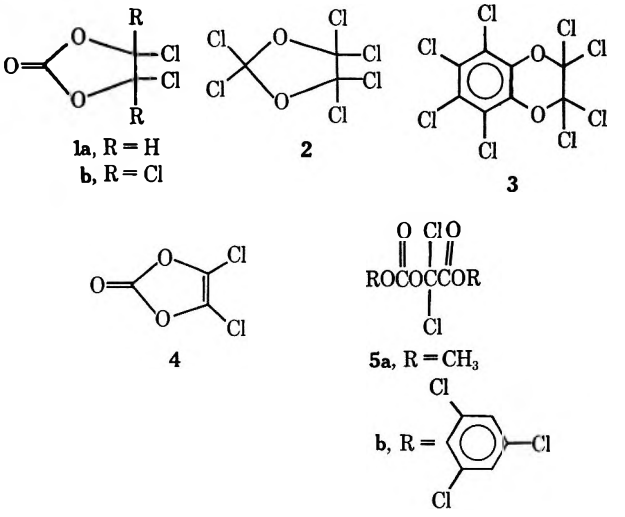
TABLE I

CHEMILUMINESCENCE OF **1b**, **4**, AND **5**[a,b]

Expt	Compd, *M*	H_2O_2, *M*	Quantum yield, 10^2 einstein mol^{-1}	Lifetime,[c] $T_{3/4}$, min	I_{max}[d]
1	**1b**, 0.03	0.07	0.98	8	9.2
2	**1b**, 0.03	0.03	0.85	17	3.7
3	**1b**, 0.10	0.23	0.21	4	12.5
4	**4**, 0.03	0.07	0.89	16	2.8
5	**5a**, 0.10	0.25	0.04	8	0.6
6	**5b**, 0.03	0.37	0.75	12	4.6
7	**1b**, 0.04	b	4.92	41	9.6
8[e]	**1b**, 0.04	b	4.92	108	9.1
9[f]	**1b**, 0.04	b	6.49	65	13.0
10	**1b**, 0.10	b	2.29	46	24.2
11	**1b**, 1.0	b	0.19	10	68.3
12	**4**, 0.04	b	3.40	94	2.2
13	**4**, 0.10	b	2.30	147	4.3
14	**5b**, 0.03	b	...	20	0.6

[a] Reaction of ester, 98% H_2O_2, and 2.3×10^{-3} *M* 9,10-bis-(phenylethynyl)anthracene (BPEA) in 75% ethyl benzoate and 25% *tert*-butyl alcohol. [b] Hetergeneous reaction of three parts (by volume) ester and 4×10^{-3} *M* BPEA with one part 30% aqueous H_2O_2. [c] Time required for emission of 75% of total light. [d] Maximum intensity in foot-lamberts cm^{-1}. [e] Initial concentration of BPEA was 1.3×10^{-3} *M*. After 60 min of reaction time more BPEA was added to make final concentration 4×10^{-3} *M*. [f] Solvent for **1b** and BPEA was diethyl carbonate.

obtained when 0.03 *M* **1b** was allowed to react with 98% H_2O_2 in a solution of 75% ethyl benzoate and 25% *tert*-butyl alcohol which contained 3×10^{-3} *M* 9,10-bis-(phenylethynyl)anthracene (BPEA).[2] Moreover, in a two-phase system in which a solution of **1b** and BPEA in diethyl carbonate was stirred with 30% aqueous H_2O_2 (expt 9), a chemiluminescence efficiency of 6.5% was measured. Thus, in a homogeneous system the chemiluminescence efficiency of **1b** is comparable with the 1% reported for electronegatively substituted oxamides[3] and the well-studied reaction of luminol with hydrogen peroxide.[4] Under the best conditions, however, the reaction of **1b** with H_2O_2 is the most efficient nonbiological chemiluminescent reaction reported, with the exception of certain diaryl oxalates (8% at 0.03 *M*).[5]



The related chlorinated ethylenedioxy derivatives **1a**, **2**, and **3**, and esters **4** and **5** which were prepared from **1b** also produced light when allowed to react with H_2O_2 in the presence of BPEA. In 75% ethyl benzoate and 25% *tert*-butyl alcohol the chemiluminescence efficiencies of dichlorovinylene carbonate (**4**) and ester **5b** were 0.75–0.89%, and in a heterogeneous system the efficiency of **4** was 3.4% (see expt 4, 6, and 12). Maximum intensities of only 0.3–0.5 foot-lamberts cm^{-1} and lifetimes of 4–18 min could be obtained with dichloroethylene carbonate (**1a**), perchloro-1,3-dioxolane (**2**), and perchloro-1,4-benzodioxane (**3**) in 75% ethyl benzoate and 25% 3-methyl-3-pentanol, although in a two-phase system **3** did provide light for 1 hr (maximum intensity, 2.3 foot-lamberts cm^{-1}). It is therefore apparent from these experiments that the carbonyl and tetrachloroethylenedioxy groups in **1b** are required for efficient chemiluminescence.

A comparison of expt 1, 3, 7, 10, and 11 in Table I indicates that the chemiluminescence efficiency of **1b** is reduced at higher ester concentration. At least part of the quenching is due to the decomposition of fluorescer, since in 0.10 *M* **1b** systems unreacted carbonate was still present when BPEA fluorescence could no longer be detected by irradiation of the reaction solution with uv light. Other fluorescers such as 9,10-diphenylanthracene, rubrene, and perylene were similarly destroyed in the reaction of **1b** with H_2O_2. The development of a highly acidic medium resulting from by-product hydrogen chloride may contribute to concentration quenching, since a similar effect is observed in the chemiluminescent reaction of oxalyl chloride and hydrogen peroxide.[6] The use of weak bases, however, such as sodium acetate, sodium bicarbonate and sodium carbonate, or a phosphate buffer in the 30% aqueous peroxide solution gave no appreciable enhancement of light output.

The existence of a long-lived intermediate is indicated by a comparison of the results of expt 7 and 8 in Table I, which are also illustrated in Figure I. In expt 7 the concentration of BPEA at the beginning of the reaction was 4×10^{-3} *M* and was sufficient to maintain continuous emission. In expt 8 the initial concentration of BPEA was 1.3×10^{-3} *M* and no light was detected after 22 min. Additional BPEA was added after 60

(1) The emitting species is the first excited singlet state of the fluorescer, since the chemiluminescence emission spectrum matched the fluorescence emission curve in each reaction reported here.

(2) D. R. Maulding and B. G. Roberts, *J. Org. Chem.*, **34**, 1734 (1969).

(3) D. R. Maulding, R. A. Clarke, B. G. Roberts, and M. M. Rauhut, *ibid.*, **33**, 250 (1968).

(4) Karl-Dietrich Gundermann, "Chemilumineszenz organischer Verbindungen," Springer-Verlag, West Berlin and Heidelberg, 1968, p 63.

(5) M. M. Rauhut, *Accounts Chem. Res.*, 80 (1969).

(6) M. M. Rauhut, B. G. Roberts, and A. M. Semsel, *J. Amer. Chem. Soc.*, **88**, 3604 (1966).

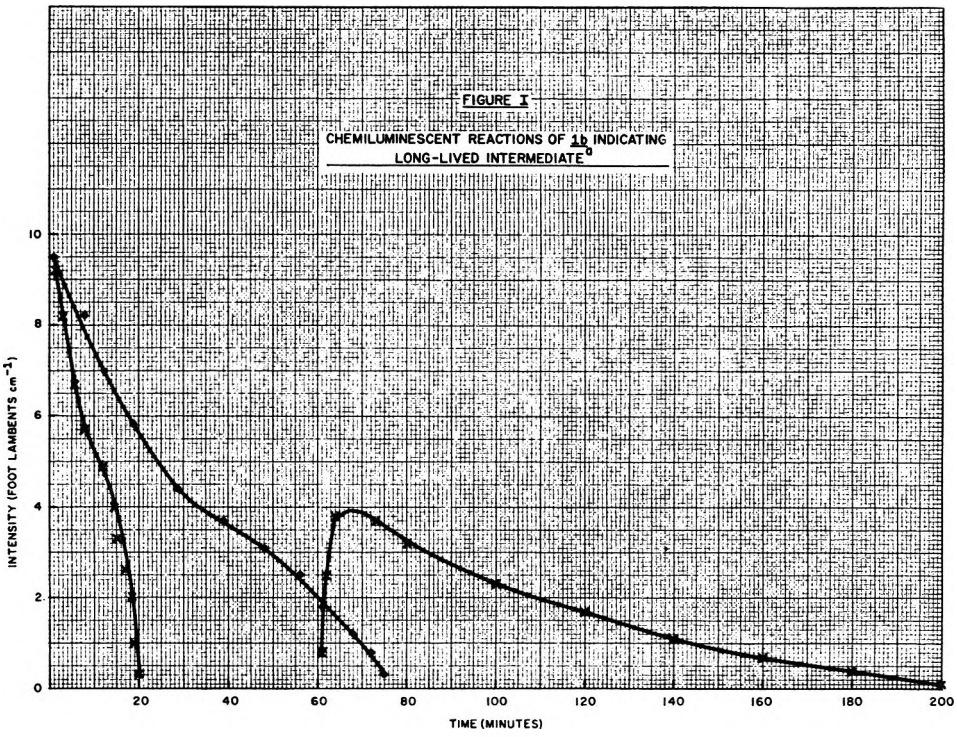
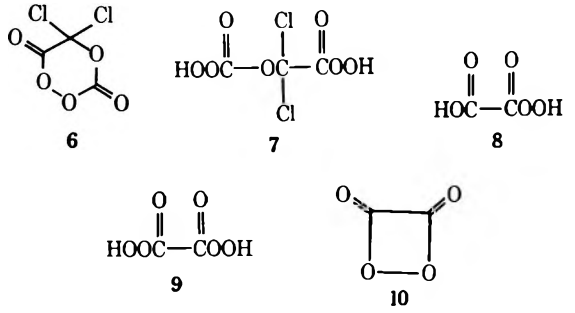


Figure 1.—Plot of the intensity-time values obtained in expt 7 and 8 described in Table I. The decay curve for expt 7 is represented by (●—●) and the curve for expt 8 by (×—×).

min of reaction time, so that the final concentration of fluorescer was 4×10^{-3} *M*. Even though the emission of light in expt 8 was interrupted, the quantum yields of the two reactions are similar.



By analogy with the reaction of **1b** with methanol,[7] initial attack at the carbonyl is expected in the chemiluminescent reaction of **1b** with H_2O_2, rather than displacement of a *gem*-dichloromethyl group. Thus the cyclic peroxide **6** and the diperoxy acid **7** may be key intermediates, although further reaction of **6** or **7** with 30% or 98% H_2O_2 to give monoperoxyoxalic acid (**8**), diperoxyoxalic acid (**9**), or 1,2-dioxetanedione (**10**), which have been proposed as intermediates in peroxyoxalate chemiluminescence,[5] presently can not be ruled out.

Experimental Section

In the chemiluminescence experiments 1,2-dichloroethylene carbonate supplied by J. T. Baker Chemical Co. was used without purification. Tetrachloroethylene carbonate (**1b**),[8] dichlorovinylene carbonate (**4**),[9] and the dichloroglycolates **5a** and **5b**[7] were prepared by the reported procedures.

Hexachloro-1,3-dioxolane (**2**).—Chlorine was bubbled into a refluxing solution of 7.4 g (0.10 mol) of 1,3-dioxolane and 100 ml of carbon tetrachloride, while the solution was irradiated with a Hanovia 100-W lamp (Pyrex filter) until a yellow-green color persisted. The solvent was removed by evaporation and the resulting oil was distilled twice, bp 78° (5 mm). The yield of the colorless product was 38%; ir 1010 cm^{-1}; nmr, no peaks; mass spectrum *m/e* 243 (M − Cl).

Anal. Calcd for $C_3Cl_6O_2$: C, 12.81; Cl, 75.80. Found: C, 13.15; Cl, 75.62.

Octachloro-1,4-benzodioxane (**3**).—Chlorine was bubbled into a refluxing solution of 1.55 g of 5,6,7,8-tetrachloro-1,4-benzodioxane[10] in 200 ml of carbon tetrachloride while the solution was irradiated with a Hanovia 100-W lamp (Pyrex filter) until a yellow-green color persisted. Evaporation of solvent gave 2.2 g (95%) of colorless solid, mp 128–130°.

Anal. Calcd for $C_8Cl_8O_2$: C, 23.30; Cl, 68.93. Found: C, 23.02; Cl, 68.65.

Chemiluminescence Emission Measurements.—Procedures and instrumentation for the determination of absolute emission intensities, spectra and quantum yields have been described previously.[11] The chemiluminescent reactions were initiated by injecting an aliquot of stock hydrogen peroxide solution from an all-glass syringe into solutions of the chlorinated ethylenedioxy derivative and fluorescer in a stirred 3-ml circular cuvette attached to a spectroradiometer. The data from the radiometer was converted to foot-lamberts cm^{-1} by a Scientific Data 925 computer programmed with the calibration data.

Registry No.—**1b**, 22432-68-4; **2**, 34288-86-3; **3**, 34288-87-4; **4**, 17994-23-9; **5a**, 33619-75-9; **5b**, 33661-49-3.

Acknowledgment.—This work was supported by the Naval Ordnance Laboratory, Silver Spring, Md. The authors wish to thank Dr. M. M. Rauhut for his helpful comments.

(7) D. R. Maulding, *Synthesis*, 480 (1971).
(8) E. K. Ellinghoe and L. R. Melby (to Du Pont), U. S. Patent, 2,816,287 (1957); *Chem. Abstr.*, **52**, 12899 (1958).
(9) H. D. Scharf, W. Droste, and R. Liebig, *Angew. Chem., Int. Ed., Engl.*, **7**, 215 (1968).
(10) L. Horner and H. Merz, *Justus Liebigs Ann. Chem.*, **570**, 89 (1950).
(11) M. M. Rauhut, *et. al.*, *J. Amer. Chem. Soc.*, **89**, 6515 (1967).

Thermal and Photochemical Dimerization of Norbornadiene[1] Using Tetracarbonylnickel as a Catalyst[2]

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Thermal dimerization of olefins using transition metal complexes as catalysts have been investigated extensively,[3] but little attention has been focused on the analogous photochemical reactions.[4] As a result, few comparisons have been made between the two excitation processes. In this communication a comparison is made between thermal excitation and photochemical excitation on the $Ni(CO)_4$-catalyzed dimerization of norbornadiene. A structure is unambiguously established for one of the pseudo-Diels–Alder dimers from the photoreaction, and the effect of a cyclopropane ring on the nmr spectra of this pseudo Diels–Alder dimer is discussed.

Previous investigators[3a-f] have shown that cyclobutane dimers I and II (Figure 1) are formed from the thermal reaction of $Ni(CO)_4$ and norbornadiene. Repetition of the thermal work in neat norbornadiene at 85° confirmed the above conclusions and we would simply add that the ratio of dimers I and II is 3:1, respectively.

Photochemical excitation using a Hanovia 450-W mercury lamp equipped with a Pyrex filter, cooling jacket, and "merry-go-round" sample holder gave two pseudo-Diels–Alder dimers having the general structure III (Figure 1). These two compounds were shown by

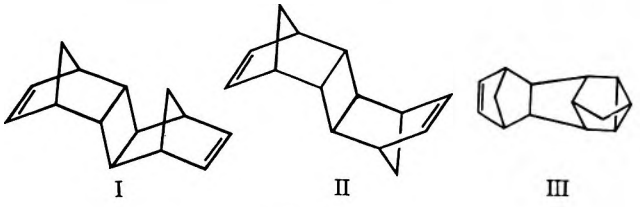

Figure 1.

gc and nmr to be identical with compounds previously prepared by Katz[3f,i] and Greco[5] through other processes. While Katz[3i] has suggested a structure for one of these dimers, we felt that a single-crystal X-ray structure analysis would accomplish two things. It would establish unambiguously the stereochemistry of

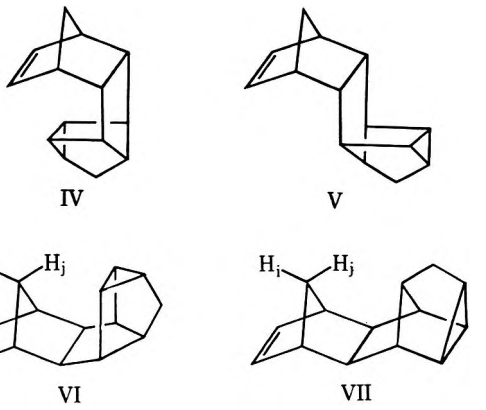

Figure 2.

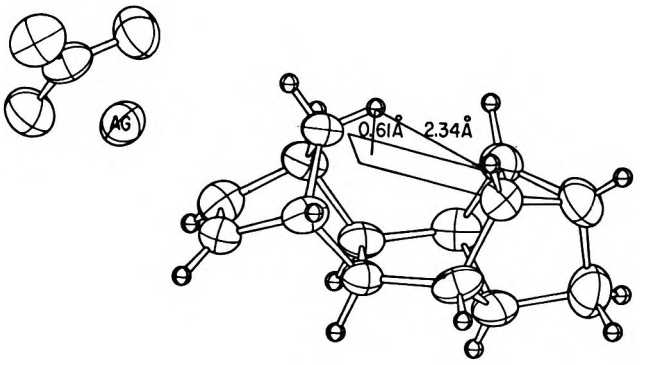

Figure 3.

one of the four possible dimer isomers which are discussed below. Furthermore, we could correlate the actual structure with its nmr spectrum which appeared to possess some useful information regarding cyclopropane interaction. We were able to show by nmr that no interconversion of cyclobutane and Diels–Alder dimers occurs under reaction conditions.

The above observations suggest that $Ni(CO)_4$ has the unusual ability to produce cyclobutane dimers thermally and pseudo-Diels–Alder dimers photochemically with norbornadiene. It is our feeling that both processes are thermal, but in the photochemical reaction a different catalytic species is being generated. Another compound, $Co(CO)_3NO$, has been shown to yield cyclobutane and pseudo-Diels–Alder dimers[3h] under thermal excitation, only which suggests that the necessary element for Diels–Alder formation is the loss of three ligands. Perhaps in the $Ni(CO)_4$ reaction light is necessary to remove the third carbon monoxide moiety. Further mechanistic investigations are continuing.

Stereochemical Assignments.—There are four possible isomers of the general structure III (Figure 2). Prior to this investigation structures IV and V had been assigned their stereochemistry,[3f] but VI and VII which were obtained from the $Ni(CO)_4$ reaction had not been assigned unambiguously. To ascertain isomer identities, the silver nitrate complex of VI[6] was prepared and subjected to X-ray crystallographic analysis. The results are shown in Figure 3.

This evidence combined with previous work establishes the stereochemistry for three of the four possible

(1) Bicyclo[2.2.1]hepta-2,5-diene.

(2) For the first paper in this area, see W. Jennings and B. Hill, *J. Amer. Chem. Soc.*, **92**, 3199 (1970).

(3) (a) R. Pettit, *ibid.*, **81**, 1266 (1959); (b) C. W. Bird, D. L. Colinese, R. C. Cookson, J. Hudec, and R. O. Williams, *Tetrahedron Lett.*, **No. 11**, 373 (1961); (c) D. M. Lemal and K. S. Shim, *ibid.*, 368 (1961); (d) L. G. Cannell, *ibid.*, 5967 (1966); (e) D. R. Arnold, D. J. Trecker, and E. B. Whipple, *J. Amer. Chem. Soc.*, **87**, 2596 (1965); (f) T. J. Katz, J. C. Carnahan, Jr., and R. Boecke, *J. Org. Chem.*, **32**, 1301 (1967); (g) F. W. Hoover and R. V. Lindsey, Jr., *ibid.*, **34**, 3051 (1969); (h) P. W. Jolly and F. G. A. Stone, *J. Chem. Soc.*, 6416 (1965); (i) T. J. Katz and N. Acton, *Tetrahedron Lett.*, 2601 (1967).

(4) (a) An excellent review article on the subject was written by G. N. Schrauzer, *Advan. Catal.*, **18**, 373 (1968); (b) D. J. Trecker, R. S. Foote, J. P. Henry, and J. E. McKean, *J. Amer. Chem. Soc.*, **88**, 3021 (1966); (c) D. J. Trecker, *et al.*, *ibid.*, **87**, 3261 (1965).

(5) A. Greco, *et al.*, *J. Org. Chem.*, **35**, 271 (1970).

(6) This major product isomer is the one labeled "predominant isomer" by Mrowca and Katz.[3i]

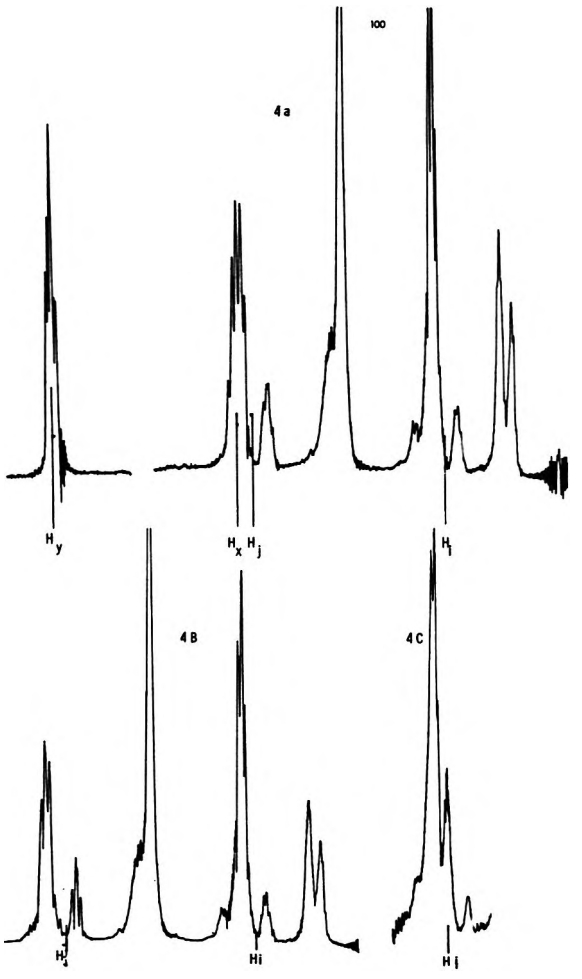

Figure 4.—Nmr spectra of isomer VI: (a) nondecoupled spectra; (b) the H_y proton decoupled from the H_j proton which is now observed as a resolved triplet;[9,10] (c) the H_j proton is decoupled from the H_i proton.

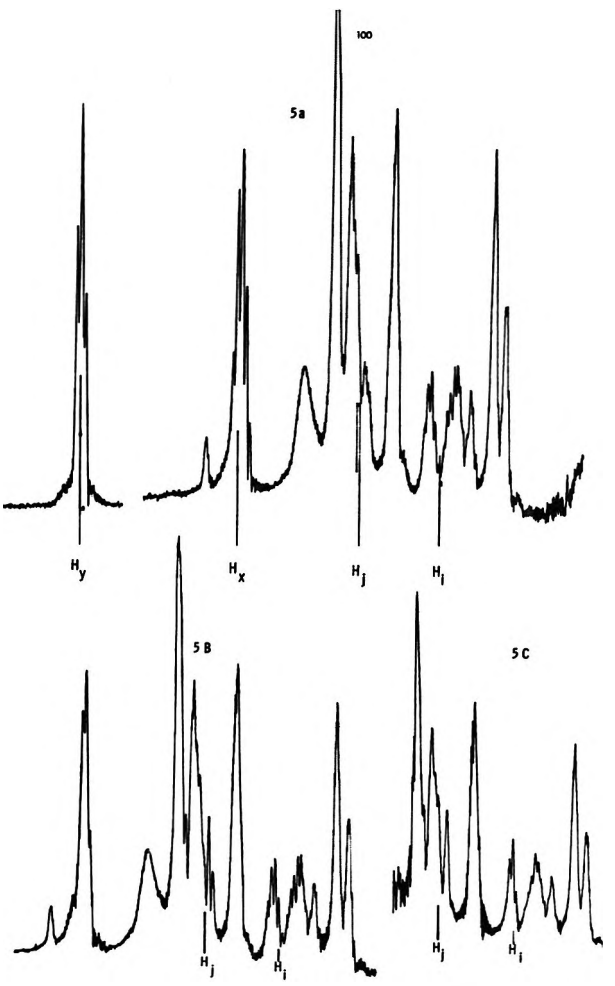

Figure 5.—Nmr spectra of isomer VII: (a) nondecoupled spectra; (b) the H_y protons are decoupled from the H_j proton which now shows only part of its triplet;[9,10] (c) the H_x protons are decoupled from the H_i and H_j protons which are collapsing toward doublets.

isomers of III. Since the fourth isomer[7] has similar ir and nmr spectra (Figure 4a and 5a) it is quite reasonably assigned to isomer VII.

Nmr Correlation.—While the X-ray analysis leaves little doubt as to the nature of isomer VI, it affords a unique opportunity for comparison between the structure and nmr spectrum. One distinct difference between isomers VI and VII (Figure 2) is the relative positions of the H_j protons with respect to the cyclopropane ring in the other nortricyclene moiety. We reasoned that either the H_i or H_j proton would be affected by the adjacent cyclopropane ring in VI, but unaffected in isomer VII. Furthermore, the effect might add evidence as to the nature of a ring current in cyclopropanes. The H_i and H_j bridge protons (Figure 6) can be characterized as an AX quartet with a coupling constant of ≈ 10 cps. By decoupling the H_X from H_i protons, we were able to determine signals belonging to H_i and H_j. Furthermore, the H_y protons are long range coupled to the H_j ones[8-10] and, thus, decoupling further facilitated the peak assignments for H_j and H_i (Table I). The doublets of the quartet are sufficiently separated for individual proton assignment. Portions of the decoupled spectra of isomers VI and VII are shown in Figures 4 and 5.

TABLE I

Isomer	—Nmr ($DCCl_3$), ppm— H_j	H_i	Difference
VI	2.43	1.15	1.28
VII	1.80	1.17	0.63

As suspected from the structures, the cyclopropyl ring is apparently deshielding the H_j proton in isomer VI and not in isomer VII. One cannot attribute these differences in chemical shift for the H_j proton in VI and VII to ring strain variation because the H_i proton would also be altered. A closer look at the crystal structure of VI (Figure 3) reveals that H_j lies 2.34 ± 0.04 Å from the cyclopropyl carbon–carbon bond and 0.61 Å above the projected equatorial plane of the cyclopropyl ring. Thus, it is clear that a proton in the equatorial plane of a cyclopropyl ring will experience a downfield shift suggestive of a ring current. These conclusions on cyclopropyl ring effects are in agreement with those proposed by Roberts.[11] The nmr assign-

(7) This minor product isomer is identical with that of Figure 1e of Greco.[4]

(8) (a) E. I. Snyder and B. Franzus, *J. Amer. Chem. Soc.*, **86**, 1166 (1964); (b) Franzus, et. al., *ibid.*, **90**, 3721 (1968); (c) A. P. Marchand and J. E. Rose, *ibid.*, **90**, 3724 (1968).

(9) This proton is coupled only weakly to the H_y one but exists as a triplet on decoupling because it is coupled to the two bridgehead protons (H_x).

(10) When the H_y protons are irradiated, the upfield H_i proton is unaffected.

(11) D. J. Patel, M. E. H. Howden, and J. D. Roberts, *J. Amer. Chem. Soc.*, **85**, 3218 (1963).

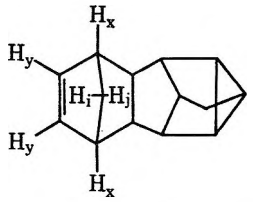

Figure 6.

ments are analogous to the work of Franzus[8] whose studies characterized this type of ring system.

We may conclude that $Ni(CO)_4$ is a unique catalyst having the ability to produce different types of norbornadiene dimers as a function of the type of excitation. Furthermore, all four Diels–Alder dimers structures are now firmly assigned and nmr interpretation of these types of structures is somewhat facilitated. Ring current effects in cyclopropane are implicated in deshielding an equatorial proton.

Experimental Section

General.—The nmr spectra were obtained from a Varian A-60 spectrometer while all the spin decoupling was done on a Varian HA-60 spectrometer. Gas chromatography information was determined by a Varian Aerograph Model 1740, and preparative separations were done on an Aerograph Autoprep Model A-700. A Varian CH-5 mass spectrometer with a gas chromatograph attached was used for mass spectral data. Norbornadiene was purchased from Frinton, purified (according to gc analysis) by recrystallizing the $AgNO_3$ complex of it in ethanol, and recovered by thermal decomposition under vacuum. The $Ni(CO)_4$ (toxic), obtained from Matheson, was distilled once prior to use.

Thermal Reaction.—To 8.5 ml of norbornadiene (7.73 g, 83.9 mmol) under oxygen-scrubbed N_2 in a flask fitted with reflux condenser and Hg bubbler was added $Ni(CO)_4$ (0.145 g, 0.849 mmol). The solution was brought to reflux (85–87°) and held there for 6.5 hr. Analysis by gc (6-ft column, 5% SE-30 on Gas-Chrom Z, 100–120 mesh) showed two dimer peaks in the ratio (peak heights) of 3:1. The dimers (3.17 g, 17.2 mmol) constituting a 41% conversion of norbornadiene [2030% yield based on $Ni(CO)_4$] were removed from solution by distillation under vacuum. Comparison of the nmr spectrum of the mixture with those of dimers I and II reported in the literature[5e] proved their identity. The integration of the olefin proton peaks in the nmr spectrum also showed a relative ratio of 3:1 I:II.

Photochemical Reaction.—Under vacuum (<0.015 mm) purified norbornadiene was transferred into a calibrated flask and 8.5 ml (7.73 g, 83.9 mmol) was transferred into a Vycor tube (10-mm i.d., 20-cm length). $Ni(CO)_4$ (0.145 g, 0.849 mmol) was added to the norbornadiene *via* syringe through a septum above the tube which was then sealed under vacuum and irradiated for 4.5 days in a "merry-go-round" tube holder by a Hanovia 450-W Hg lamp in a quartz, water-cooled jacket. From gc analysis (6-ft column, 5% SE-30 on Gas-Chrom Z, 100–120 mesh; 6-ft column, 20% Carbowax 20M on Chromosorb W, 80–100 mesh) the contents of the tube were found to contain dimers, 90% of which were the two pseudo-Diels–Alder dimers (peak height ratio of 2:1). Also detected were a trace of CO insertion product (parent peak in mass spectrum at m/e 212) and some trimer (parent peak at m/e 276). Separation of the products by vacuum distillation produced 0.876 g (4.75 mmol) of dimers [11% conversion of norbornadiene or 559% yield based on $Ni(CO)_4$] and 43 mg (0.156 mmol) of trimer. The dimers were separated on a 20-ft column, 20% Carbowax 20M on Chromosorb W, 80–100 mesh, 190°. The nmr spectrum of the original mixture of dimers (ratio of olefin proton integrations was 2:1 VI:VII) was the same as the combination of the nmr spectrum of each of the components. When Pyrex and quartz tubes were used rather than Vycor, both ratios and amounts as well as number of products were essentially the same from gc information.

Investigation of Interconversion of Dimers.—A mixture of pseudo-Diels–Alder dimers (5.15 g), the predominant one being VI, and $Ni(CO)_4$ (91 mg) were heated at 92° for 26 hr under nitrogen. An nmr spectrum showed the dimer mixture to be unchanged. Likewise, a mixture of dimers I and II (6.33 g) and $Ni(CO)_4$ (104 mg) were sealed under vacuum and irradiated as above for 1 week. The nmr analysis showed no change in dimer contents.

Silver Nitrate–Dimer Complex for Crystal Structure.—To dimer VI a saturated aqueous $AgNO_3$ solution was added and the resulting white precipitate collected. After being washed with water the precipitate was recrystallized from absolute ethanol and crystals were used for structure determination.

X-Ray Data.—This compound crystallizes in the monoclinic space group $P2_1/c$ with cell dimensions a = 17.554(9) Å, b = 6.908(4) Å, c = 11.031(5) Å, and β = 103.10(3)°.

A unique data set was collected by the θ–2θ scan technique on a GE XRD-5 diffractometer using zirconium-filtered Mo K_α radiation. Two crystals were used to collect 1181 pieces of data, of which 841 were found to be more than twice the standard deviation of the intensity and were thus considered observed. The data were reduced and corrected for absorption.

The structure was solved by the conventional heavy atom method. Hydrogens were located from the difference map. The structure was refined using full matrix least squares, treating hydrogen atoms isotropically and nonhydrogen atoms anisotropically, to an R value of 3.3%.[12]

Registry No.—I, 2957-68-8; II, 1624-13-1; IV, 17926-98-6; V, 17926-99-7; VI, 18067-61-3; VII, 33780-58-4; norbornadiene, 121-46-0; tetracarbonylnickel, 13463-39-3.

Acknowledgment.—Authors P. W. Jennings and G. E. Voecks wish to thank Dr. William Waters for his help with the nmr work. Acknowledgment is made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, and Cities Service Oil Co. for support of this research.

(12) The complete X-ray data will be published in an appropriate journal.

The Photochemistry of 1-Keto-2-carbomethoxymethylenebenzocyclobutene

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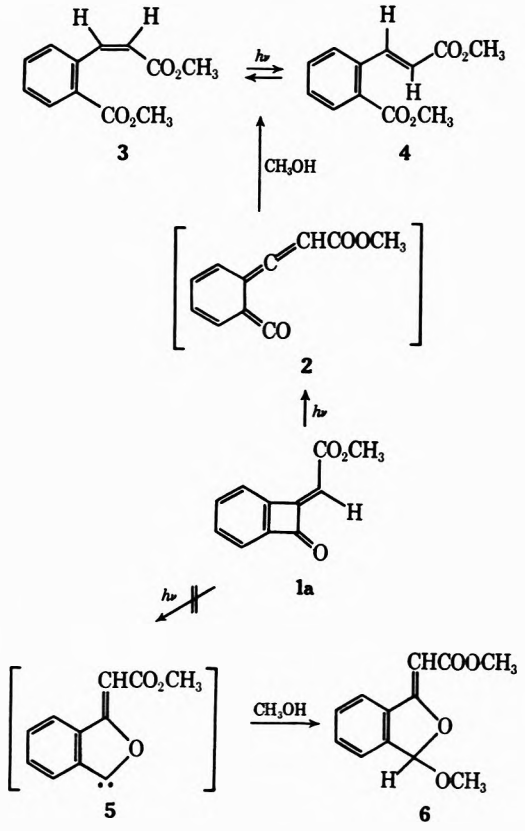
We wish to report our results on the photochemical decomposition of 1-keto-2-carbomethoxymethylenebenzocyclobutene (**1a**). This keto ester is of interest because of its relation to the recently studied 2-methylenecyclobutanones,[2] benzocyclobutenones,[3] and benzocyclobutadienequinone.[4]

Ultraviolet irradiation of a dilute methanol solution of **1a** gave, upon preparative tlc, a 15% yield of an 85:15 mixture of cis and trans methyl *o*-carbomethoxycinnamate (**3** and **4**, Scheme I), as the major reaction products. Several additional unidentified minor components were also obtained in a combined yield of 6%. The remainder of the material remained at the origin of the tlc plate as a brown gum. Esters **3** and **4** were separated by preparative gas chromatography.

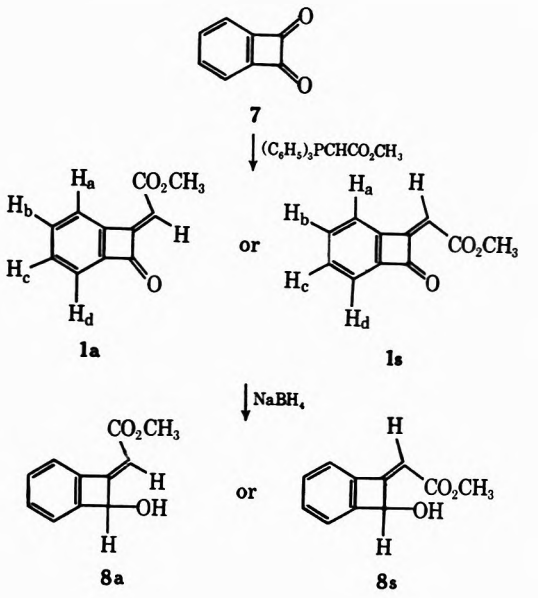
Methyl *o*-carbomethoxy-*cis*-cinnamate (**3**) showed the following spectral properties: nmr δ 3.51 (s, 3 H), 3.80

(1) NDEA Predoctoral Trainee, 1967–1970.
(2) D. R. Morton, E. Lee-Ruff, R. M. Southam, and N. J. Turro, *J. Amer. Chem. Soc.*, **92**, 4349 (1970).
(3) M. P. Cava and R. J. Spangler, *ibid.*, **89**, 4550 (1967).
(4) H. A. Staab and J. Ipaktschi, *Chem. Ber.*, **101**, 1457 (1968).

SCHEME I



SCHEME II



(s, 3 H), 5.99 (d, 1 H, J = 12 cps), 7.20–7.64 (m, 4 H), 7.92–8.08 (m, 1 H); decoupling at δ 5.99 collapsed two peaks at 7.47 and 7.59 to a single peak at 7.53; uv λ_{max} 216 nm (log ϵ 4.10), 284 (3.47); ir (KBr pellet) 2945, 1729, 1717, 1635, 1482, 1434, 1394, 1297, 1268, 1199, 1161, 1134, 1080, 821, 758, and 708 cm^{-1}; mass spectrum m/e (rel intensity) 220 (4), 205 (2), 189 (8), 173 (12), 161 (100), 146 (5), 145 (6), 130 (6), 129 (7), 118 (9). Methyl *o*-carbomethoxy-*trans*-cinnamate (**4**) showed these properties: nmr δ 3.78 (s, 3 H), 3.90 (s, 3 H), 6.27 (d, 1 H, J = 16 cps), 7.24–7.64 (m, 3 H), 7.82–8.03 (m, 1 H), 8.45 (d, 1 H, J = 16 cps); uv λ_{max} 224 nm (log ϵ 4.12), 271 (4.06); ir (KBr pellet) 2950, 1717, 1638, 1482, 1436, 1321, 1260, 1196, 1175, 1132, 1080, 977, 763, 719 cm^{-1}; mass spectrum identical with that of cis isomer **3**. These spectra are fully consistent with the assigned structures; furthermore trans diester **4** was identical with an authentic sample prepared by the method of Elvidge and Jones.[5] Irradiation of a solution of pure **4**[5] for 58 hr with a 350-nm light source smoothly yielded an 85:15 mixture of **3** and **4**, identical with the mixture of **3** and **4** obtained upon irradiation of **1a**. Keto ester **1a** was found to be stable toward refluxing methanol in the dark.

Thus, the major observable photodecomposition pathway of **1a** appears to be an initial ring opening to give the *o*-benzoquinone intermediate **2**. By analogy with the photochemistry of benzocyclobutadienequinone (**7**)[4] we feel that *o*-quinone **2** is a likely intermediate, although there is no direct proof for its existence. Ring opening is then followed by reaction of the intermediate **2** with the solvent, methanol, to give the methyl *o*-carbomethoxycinnamates (**3** and **4**). These in turn are in photoequilibrium with each other (Scheme I). Significantly, we did not detect any of the acetal **6**, the product to be expected if **1a** underwent a photochemical ring expansion to the oxacarbene **5** in a manner analogous to that of numerous cyclobutanones[2] and benzocyclobutadienequinone (**7**).[4]

Compound **1** was synthesized by the method of Cava and Pohl[6] from benzocyclobutadienequinone (**7**) and triphenylphosphinecarbomethoxymethylene (Scheme II). However, the stereochemistry about the double bond of **1** was not determined by these workers. The heretofore unreported nmr spectrum of **1** showed a singlet (3 H) at δ 3.86, a singlet (1 H) at 6.16, a multiplet (3 H) at 7.56–7.83, and a multiplet (1 H) at 8.26–8.38. This spectrum is consistent with the anti isomer **1a** and not the syn isomer **1s**, in that one of the aromatic protons is clearly deshielded relative to the remaining three. We attribute this deshielding to the proximity of H_a (Scheme II) to the ester carbonyl group. That this deshielding is not due to the proximity of H_d (Scheme II) to the ketone carbonyl is clear from examining the nmr spectra of other benzocyclobutenones. For example, the nmr spectrum of benzocyclobutenone itself consists of a broad aromatic multiplet centered at δ 7.33 in which the proton ortho to the carbonyl function is not deshielded relative to the other three aromatic protons. To further substantiate this conclusion, **1** was reduced with sodium borohydride to the alcohol **8** (Scheme II). The infrared spectrum of **8**, determined at several concentrations in carbon tetrachloride solution, showed no evidence of intramolecular hydrogen bonding. This behavior is to be expected from the anti isomer **8a** but not from the syn isomer **8s**. Thus we are confident that **1** is of anti stereochemistry, as depicted in **1a**.

Experimental Section

General.—A Rayonet photochemical reactor Model RPR-100 equipped with a 350-nm light source was used for irradiations. Ir spectra were determined with a Perkin-Elmer Model 621 spectrometer. Nmr spectra were determined with a Varian HA-100 or a Varian A-60 spectrometer. Uv spectra were determined in methanol solution with a Perkin-Elmer Model 202

(5) J. A. Elvidge and D. E. H. Jones, *J. Chem. Soc. C*, 2059 (1967).

(6) M. P. Cava and R. J. Pohl, *J. Amer. Chem. Soc.*, **82**, 5242 (1960).

spectrometer. Mass spectra were determined with a Hitachi Perkin-Elmer RMU 6E mass spectrometer at 70 eV. Carbon and hydrogen analyses were determined with a Perkin-Elmer Model 240 elemental analyzer at the University of Idaho.

Photolysis of 1-Keto-2-carbomethoxymethylenebenzocyclobutene[6] (1a) in Methanol Solution.—To a quartz vessel were added 139 mg (0.740 mmol) of 1-keto-2-carbomethoxymethylenebenzocyclobutene (1a) and 20 ml of methanol. The reaction vessel was then flushed with nitrogen and the system was closed. The solution was then irradiated at 350 nm and the reaction was monitored with gas chromatography. After 28 hr gc showed that the starting material had all reacted and the irradiation was stopped. The methanol was then removed by a rotary evaporator. The residue was dissolved in chloroform and streaked on an 8 in. × 8 in. × 1000 μ preparative thin layer plate of neutral alumina previously oven dried for 2 hr. The plate was developed with chloroform, and the main band (R_f 0.77) was removed from the plate and extracted with several portions of chloroform to give 24 mg (0.109 mmol, 15% yield) of cis and trans methyl *o*-carbomethoxycinnamate (**3** and **4**). Gas chromatography indicated that the cis:trans ratio was 85:15. Pure **3** and **4** were obtained by preparative gas chromatography using a 10 ft × 1/4 in. 5% SE-30 column at 195°.

In addition to the methyl *o*-carbomethoxycinnamates isolated, several minor bands were removed from the thin layer plate and extracted with chloroform. Solvent removal gave a total of 8 mg of material which was not characterized. The remainder of the material remained as a brown band at the origin of the thin layer plate and was also not characterized.

Photoisomerization of Methyl *o*-Carbomethoxy-*trans*-cinnamate(4).—To a quartz nmr tube was added 2 drops of methyl *o*-carbomethoxy-*trans*-cinnamate (**4**)[5] followed by several drops of deuteriochloroform with 1% tetramethylsilane. The reaction mixture was then put under a nitrogen atmosphere and sealed with an nmr cap. The mixture was then irradiated at 350 nm and the reaction was monitored with nmr. After 58 hr both nmr and gc analysis showed the solution contained a mixture of 85% cis cinnamate **3** and 15% trans cinnamate **4**.

Pure cis-cinnamate (**3**) was obtained by preparative gas chromatography using a 10 ft × 1/4 in. 5% SE-30 column at 195°. Reinjection of a small amount of the collected material indicated high (97+%) purity and that no isomerization to trans-cinnamate (**4**) had occurred on gc.

Thermal Reaction of 1-Keto-2-carbomethoxymethylenebenzocyclobutene (1a) with Methanol.—To a 10-ml flask equipped with reflux condenser, drying tube, magnetic stirrer, and heating mantle were added 25 mg of 1a and 5 ml of methanol. Aluminum foil was wrapped around the reaction flask and condenser to prevent any light-induced reaction from occurring. The solution was then refluxed for 48 hr.

After solvent removal, gc analysis showed that the residue had a retention time identical with that of authentic 1-keto-2-carbomethoxymethylenebenzocyclobutene (1a). The nmr spectrum was also identical with that of authentic keto ester 1a and, furthermore, no peaks corresponding to either cis or trans methyl o-carbomethoxycinnamate (**3** or **4**) were detected.

1-Hydroxy-2-carbomethoxymethylenebenzocyclobutene (8a).—To a 50-ml flask equipped with magnetic stirrer were added 150 mg (0.615 mmol) of 1-keto-2-carbomethoxymethylenebenzocyclobutene (1a) and 15 ml of methanol. The solution was stirred at room temperature until 1a was dissolved and then 6 mg (0.63 meq) of sodium borohydride was added to the mixture with stirring. Stirring was continued for 0.5 hr. Dilution with water, extraction with chloroform, drying, and solvent removal gave 177 mg (0.615 mmol) of crude **8a** in a quantitative yield, as a thick, light yellow oil. Analysis by gc showed that the crude alcohol was 95+% pure and was contaminated with a slight amount of the keto ester starting material. Collection by gc using a 10 ft × 1/4 in. 10% SE-30 column at 183° gave **8a** as a light yellow viscous liquid (*Anal.* Calcd: C, 69.46; H, 5.30. Found: C, 69.65; H, 5.35%.): nmr δ 3.60 (s, 3 H), 4.10 (d, 1 H, J = 9 cps, shifted and collapsed to a singlet when H^+ was added), 5.36 (d, 1 H, J = 9 cps, collapsed to singlet when H^+ was added), 5.67 (s, 1 H), 7.16–7.38 (m, 3 H), 7.55–7.79 (m, 1 H); mass spectrum *m/e* (rel intensity) 190 (40), 175 (43), 158 (15), 131 (100), 130 (24), 103 (66), 102 (37), 77 (58), 51 (29). The ir spectrum determined from a 0.25 M solution of **8a** in carbon tetrachloride showed a broad (hydrogen bonded) hydroxyl absorption centered at 3450 cm^{-1} with a very small sharp band (nonhydrogen bonded) at 3590 cm^{-1}. In spectra determined at 0.025 and 0.0025 M, the broad band centered at 3450 cm^{-1} became much smaller and almost disappeared while the sharp band at 3590 cm^{-1} grew more intense upon dilution.

Registry No.—**1a**, 34288-39-6; **3**, 34288-40-9; **4**, 18454-56-3; **8a**, 34288-77-2.

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A New Synthesis of the 1,3-Thiazine Ring System

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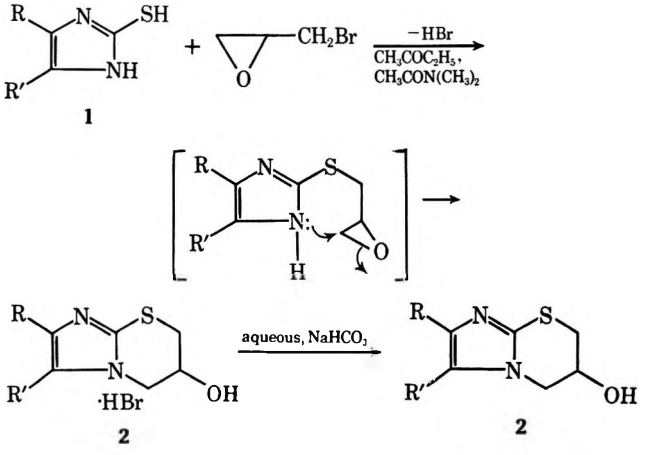
Received October 27, 1971

This note describes a simple synthesis of the 1,3-thiazine ring system, some derivatives of which have been shown to exhibit important physiological activity.[2] We became interested in these heterocycles while investigating the products obtained from the reaction of 2-mercaptobenzimidazole with α-halo ketones.[3] It seemed reasonable that treatment of this and related mercaptoazoles (**1**) with epoxy halides such as epibromohydrin would result in condensation followed by intramolecular cyclization to give the thiazine derivative **2** with the hydroxyl group on a ring carbon.



R = R′ = C_6H_5, H, C_4H_4, $C_2H_2N_2$

The hydroxyl functionality would be a handle for preparing numerous other potentially useful thiazines.

Treatment of 4,5-diphenyl-2-mercaptoimidazole[4a] (**1**, R = R′ = C_6H_5) with epibromohydrin in a mixture of 2-butanone and *N*,*N*-dimethylacetamide (10:1) at 85° for 2 hr gave the hydrobromide salt of **2** from which

(1) National Science Foundation Undergraduate Research Participant.

(2) For example, see R. M. Gesler and A. R. Surrey, *J. Pharmacol. Exp. Ther.*, **122**, 4 (1958); A. R. Surrey, W. G. Webb, and R. M. Gesler, *J. Amer. Chem. Soc.*, **80**, 3469 (1958); B. Loder, G. G. F. Newton, and E. P. Abraham, *Biochem. J.*, **79**, 408 (1961); J. C. Wilson, R. N. Downer, and H. E. Sheffer, *J. Heterocycl. Chem.*, **7**, 955 (1970).

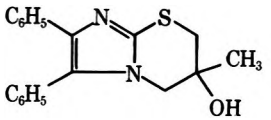
(3) H. Alper, E. C. H. Keung, and (in part) R. A. Partis, *J. Org. Chem.*, **36**, 1352 (1971).

(4) (a) Aldrich Chemical Co., Milwaukee, Wis.; (b) Pfaltz and Bauer, Inc., New York, N. Y.

6-hydroxy-2,3-diphenyl-6,7-dihydro-5*H*-imidazo[2,1-*b*]-[1,3]thiazine (**2**, R = R′ = C_6H_5) could be isolated in 48% yield (based on **1**) by basification with aqueous sodium bicarbonate. Structure **2** (R = R′ = C_6H_5) was assigned on the basis of analytical data and spectral results (see Experimental Section). For instance, the infrared spectrum (KBr) of the fused thiazine showed a broad band centered at 3150 cm^{-1} for the hydrogen-bonded OH stretching vibration and an intense band at 1068 cm^{-1} due to C–O stretching. The mass spectrum gave a parent peak at *m/e* 308 with important fragment ions at *m/e* 290, 276, 264, 204, and 178. Oxidation of **2** (R = R′ = C_6H_5) with chromium trioxide in pyridine gave the corresponding ketone ($\nu_{C=O}$ 1715 cm^{-1}). A mixture of alkenes was obtained by dehydration of **2** (R = R′ = C_6H_5) with phosphorus oxychloride in pyridine.

The dihydrothiazines **2** (R, R′ = H) (23% yield), C_4H_4 (41%), and $C_2H_2N_2$ (12%) were obtained in the same manner as that described for **2** (R = R′ = C_6H_5) by the reaction of epibromohydrin with 2-mercaptoimidazole,[4b] 2-mercaptobenzimidazole,[4a] and 8-mercaptopurine,[4a] respectively. In the latter example, cyclization may occur at the 7 or 9 nitrogen and we have, thus far, been unable to distinguish between the two possible isomers.

We have used **1** (R = R′ = C_6H_5) for studying this reaction with a variety of epoxy bromides. Treatment of the mercaptoazole with the readily prepared 1-bromo-2,3-epoxy-2-methylpropane[5] and *threo*-3-bromo-1,2-epoxybutane[6] gave 6-hydroxy-6-methyl-2,3-diphenyl-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]thiazine (**3**, 24% yield), and *erythro*-6-hydroxy-7-methyl-2,3-diphenyl-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]thiazine (**4**, 38% yield), respectively. These heterocycles are the expected



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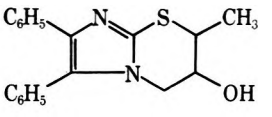
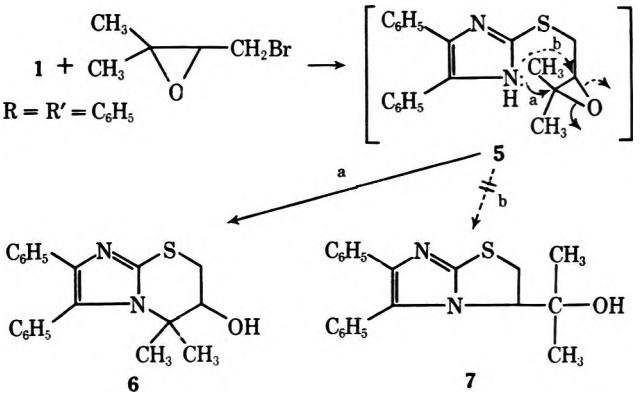


4

products arising from nucleophilic attack at the least substituted carbon of the epoxide ring.[7] However, use of 1-bromo-2,3-epoxy-3-methylbutane[8] as the epoxy halide gave **6** (31%) rather than the anticipated product, **7**. The nmr spectrum of the product showed a doublet at 5.75 ppm (–OH), which disappeared upon addition of trifluoroacetic acid. Oxidation of **6** with chromium trioxide in pyridine gave the corresponding ketone ($\nu_{C=O}$ at 1718 cm^{-1}). A six-membered rather than a five-membered ring intermediate has been invoked to explain the position of nucleophilic attack (at the least substituted carbon) in the reaction of glycidyl ethers with dibutylamine.[7] It is possible that the formation of a six-membered ring (leading to **6**) rather than the less favored five-membered ring intermediate (leading to **7**) is responsible for nucleophilic attack at the most substituted carbon of epoxide **5** (*i.e.*, path a rather than path b). These



examples demonstrate the ease with which one could place methyl groups at different saturated carbons of the thiazine ring by using the appropriate epoxy halide. It should be pointed out that no attempt was made to optimize yields in any of the reactions.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Elemental analyses were carried out by PCR, Inc., Gainesville, Fla. Infrared spectra were recorded on Perkin-Elmer 457 and 521 spectrophotometers; the wavelength readings were calibrated with polystyrene film. Nuclear magnetic resonance spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as internal standard. Mass spectra were recorded on a MS-9 spectrometer.

General Procedure for Reaction of Mercaptoazoles and Epoxy Bromides.—The mercaptoimidazole (15.6 mmol) and the epoxy halide (15.6 mmol) were suspended in a mixture of 2-butanone (150 ml) and *N*,*N*-dimethylacetamide (15 ml) and heated to 80–95° (oil bath temperature) where the solution became clear. After 1–9 hr, the precipitated hydrobromide salt (**2**·HBr) was filtered and dried. The salt was suspended in water (250–350 ml), heated to boiling (*N*,*N*-dimethylacetamide added to bring into solution water-insoluble salts), and then basified with 5% aqueous $NaHCO_3$. The resulting white precipitate was filtered and recrystallized from either 70% aqueous ethanol or acetonitrile to give the following derivatives of **2**.

A.—**2** (R = R′ = C_6H_5) had mp 219–220°; ν_{max} (KBr) 3150 (OH, broad) and 1068 cm^{-1} (CO); nmr [dimethyl sulfoxide-d_6 (DMSO-d_6)] δ 3.25 (m, 2 H, NCH_2), 3.69 (m, 2 H, SCH_2), 4.29 (m, 1 H, CH–), 5.59 (d, 1 H, OH), and 7.02–7.41 (m, 10 H, ArH). Addition of trifluoroacetic acid resulted in disappearance of the δ 5.59 doublet. The mass spectrum gave a parent ion peak at *m/e* 308 as well as fragments at *m/e* 290, 276, 264, 204, and 178.

Anal. Calcd for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.08. Found: C, 69.98; H, 4.95; N, 9.15.

B.—**2** (R = R′ = H) had mp 202–203°; ν_{max} (KBr) 3100 (OH, broad) and 1041 cm^{-1} (CO); the mass spectrum gave a parent ion peak at *m/e* 156.

Anal. Calcd for $C_8H_8N_2OS$: C, 46.13; H, 5.16; N, 17.94. Found: C, 46.16; H, 5.04; N, 18.17.

C.—**2** (R = R′ = C_4H_4) (from 2-mercaptobenzimidazole) had mp 215–217°; ν_{max} (KBr) 3090 (OH, broad) and 1042 or 1078 cm^{-1} (CO); the mass spectrum gave a parent ion peak at *m/e* 206.

Anal. Calcd for $C_{10}H_{10}N_2OS$: C, 58.22; H, 4.90; N, 13.58. Found: C, 57.95; H, 5.24; N, 13.58.

D.—**2** (R = R′ = $C_2H_2N_2$) (from 8-mercaptopurine) had mp 215–217°; ν_{max} (KBr) 3090 (OH, broad) and 1029 or 1074 cm^{-1} (CO); the mass spectrum gave a parent ion peak at *m/e* 208.

Anal. Calcd for $C_8H_8N_4OS$: C, 46.14; H, 3.87; N, 26.91. Found: C, 46.00; H, 3.87; N, 27.05.

E.—**3** had mp 218–220°; ν_{max} (KBr) 3270 (OH, broad) and 1108 cm^{-1} (CO); nmr (DMSO-d_6) δ 1.31 (s, 3 H, CH_3), 3.12 (q, 2 H, NCH_2–), 3.57 (q, 2 H, SCH_2–), 5.31 (s, 1 H, OH), and 6.80–7.62 (m, 10 H, ArH). Addition of trifluoroacetic acid resulted in disappearance of the δ 5.31 absorption. The mass spectrum gave a parent ion peak at *m/e* 322.

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Anal. Calcd for $C_{19}H_{18}N_2OS$: C, 70.78; H, 5.63; N, 8.69. Found: C, 70.29; H, 5.40; N, 8.35.

F.—**4** had mp 218–219°; ν_{max} (KBr) 3120 (OH, broad) and 1047 cm^{-1} (CO); nmr (DMSO-d_6) δ 1.00 (s, 3 H, CH_3), 3.24 (m, 2 H, NCH_2), 4.11 (m, 2 H, $CHCH_3$ and CHOH), 5.67 (d, 1 H, OH), and 7.27 (center of multiplet, 10 H, ArH). Addition of trifluoroacetic acid resulted in disappearance of the δ 5.67 doublet. The mass spectrum gave a parent ion peak at *m/e* 322.

Anal. Calcd for $C_{19}H_{18}N_2OS$: C, 70.78; H, 5.63; N, 8.69. Found: C, 71.02; H, 5.54; N, 8.53.

G.—**6** had mp 237–238°; ν_{max} (KBr) 3140 (OH, broad) and 1078 cm^{-1} (CO); nmr (DMSO-d_6) δ 1.23 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 3.46 (m, 2 H, SCH_2), 3.90 (broad m, 1 H, CHOH), 5.75 (d, 1 H, OH), and bands centered at 7.14 and 7.47 (m, 10 H, ArH). Addition of trifluoroacetic acid resulted in disappearance of the δ 5.75 doublet. The mass spectrum gave a parent ion peak at *m/e* 336.

Anal. Calcd for $C_{20}H_{20}N_2OS$: C, 71.39; H, 5.99; N, 8.32. Found: C, 71.19; H, 6.16; N, 8.21.

Oxidation of 2 (R = R′ = C_6H_5) and 6.—Chromic oxide (5.1 mmol) was added, in small portions, to 8 ml of a well-stirred cold pyridine solution. The alcohol (1.7 mmol) was then added and the mixture was stirred at room temperature for 12–15 hr. The reaction mixture was poured into water and the ketone was extracted with methylene chloride. The methylene chloride extract was dried (Na_2SO_4), the solvent was evaporated *in vacuo*, and the residual oil was crystallized from pentane. Recrystallization from 70% aqueous ethanol gave analytically pure product.

A.—The oxidation product from **2** (R = R′ = C_6H_5) had mp 198–200°; ν_{max} (KBr) 1715 cm^{-1} (CO).

Anal. Calcd for $C_{18}H_{14}N_2OS$: C, 70.56; H, 4.60; N, 9.14. Found: C, 70.51; H, 4.91; N, 9.40.

B.—The oxidation product from **6** had mp 192–193°; ν_{max} (KBr) 1718 cm^{-1} (CO).

Anal. Calcd for $C_{20}H_{18}N_2OS$: C, 71.83; H, 5.43; N, 8.38. Found: C, 71.89; H, 5.87; N, 8.35.

Registry No.—**2** (R = R′ = C_6H_5), 34035-39-7; **2** (R = R′ = C_6H_5) oxidation product, 34035-40-0; **2** (R = R′ = H), 34035-41-1; **2** (R = R′ = C_4H_4), 34035-42-2; **2** (R = R′ = $C_2H_2N_2$), 34035-43-3; **3**, 34035-44-4; **4**, 34035-45-5; **6**, 34035-46-6; **6** oxidation product, 34035-47-7.

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Conversion of Allylic Alcohols to Chlorides without Rearrangement

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A recent report on the conversion of allylic alcohols to their chlorides without rearrangement[1] prompts us to report similar, limited observations made some time ago. The unique properties[2] of the triphenylphosphine–carbon tetrachloride reagent suggested its potential in specific allylic alcohol–chloride conversions. When the reaction was employed using the classic isomeric α- and γ-methallyl alcohol couple, the results substantiated our hopes based on prior experience (Table I).

TABLE I
CHLORIDE COMPOSITION FROM METHALLYL ALCOHOLS USING Ph_3P–CCl_4

Alcohol	CH_3CH=$CHCH_2Cl$	CH_3CHCl-CH=CH_2
CH_3CH=$CHCH_2OH$	100	0
$CH_3CHOHCH$=CH_2	11	89

The report of Meyers demonstrated that *primary* allylic alcohols can be converted to chlorides without formation of the secondary or tertiary isomer. Our results demonstrate that not only can the primary–primary conversion be achieved specifically, but also, and perhaps more importantly, the secondary–secondary conversion can be achieved with high specificity even in a system prone toward rearrangement.

Experimental Section[3]

3-Buten-2-ol was commercial material whose glpc trace showed no contamination by its allylic isomer. **2-Buten-1-ol** was a heart cut from distillation of commercial alcohol and was also free of its allylic isomer by glpc examination. Its nmr spectrum clearly showed a mixture of cis and trans isomers. Each alcohol (0.099 g, 1.37 mmol) was dissolved in 0.5 ml of carbon tetrachloride containing 0.36 g (1.4 mmol) of triphenylphosphine and kept at ambient temperature. After 48 hr the nmr spectrum of the 2-buten-1-ol mixture showed only a small amount of unreacted alcohol and 1-chloro-2-butene. High-gain examination showed the absence of signals at 264 Hz ($CH_3CHClCH$=CH_2). Examination by glpc showed 1-chloro-2-butene as the only chloride. Similarly, the nmr spectrum of the 3-buten-2-ol mixture showed some unreacted alcohol, a multiplet at 264 Hz, and a weak doublet at 236 and 228 Hz (CH_3CH=$CHCH_2Cl$) whose integral indicated 9% of the latter chloride. Examination by glpc showed that the chlorides consisted of 89% unrearranged secondary and 11% rearranged primary allylic chloride.

To determine whether the rearranged chloride from 3-buten-2-ol was a kinetic product or resulted from post-isomerization the following experiment was performed. To 1.00 g of alcohol in 6 ml of carbon tetrachloride was added 0.9 g of triphenylphosphine. After 4 hr an aliquot was removed and examined by glpc and another 0.9 g of phosphine was added. This was repeated twice more at intervals of 16 and 8 hr. The glpc results showed the presence of 8–12% primary chloride in all cases, suggesting that the latter was a kinetically controlled product.

Registry No.—3-Buten-2-ol, 598-32-3; *cis*-2-buten-1-ol, 4088-60-2; *trans*-2-buten-1-ol, 504-61-0; 1-chloro-2-butene, 591-97-9; 3-chloro-1-butene, 563-52-0.

Acknowledgment.—This work was supported by the National Science Foundation while the author was a guest at East Tennessee State University.

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(3) Chloride analyses were performed on a FFAP column operated at 50°. Chemical shift data are with reference to internal TMS.

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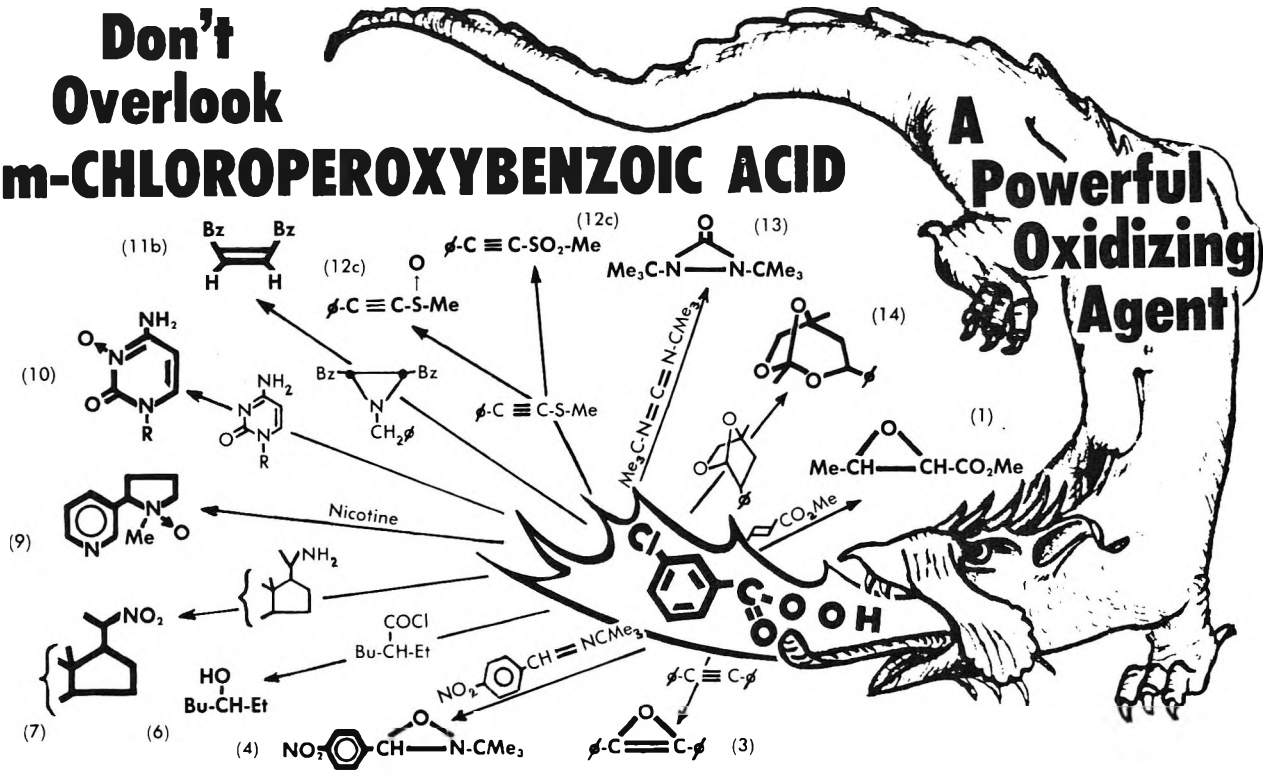
323

Don't Overlook m-CHLOROPEROXYBENZOIC ACID A Powerful Oxidizing Agent



m-CPBA is a superior oxidizing agent compared to hydrogen peroxide or other peracids in reactivity, stereoselectivity, and in purity and yield of products. Isolated **carbon-carbon double bonds** and the less reactive **α,β-unsaturated esters** are smoothly oxidized to **epoxides** in high yields.[1] In **nonconjugated dienes,** selective epoxidation occurs in the more substituted double bond.[2] Disubstituted **acetylenes** can be oxidized to **oxirenes** which break down to ketones, carboxylic acids, or esters depending on the reaction conditions.[3] Like olefins, **imines** are oxidized to the corresponding **oxaziranes.**[4]

m-CPBA is an excellent reagent for the **Baeyer-Villiger oxidation** of ketones to esters, such as acetylcyclanes[5a] and acetophenones.[5b] Related to this reaction is the conversion of **acid chlorides to alcohols in which -OH replaces -CO₂H.** For example, 3-heptanol was obtained in 73% overall yield from 2-ethylhexanoyl chloride.[6]

Primary amines can be converted to **nitroalkanes,** and the yields decrease in the order: **tert**-alkyl > **sec**-alkyl > n-alkyl.[7] **Secondary amines** give **nitroxide radicals,**[8] whereas **tertiary amines** afford the **N-oxides.**[9] Hence, nicotine is converted to the N'-oxide and to the N,N'-dioxide by 1 and 2 equivalents of m-CPBA, respectively. Among the nucleic acid bases, nucleosides, and nucleotides, only the **cytosine** and **adenine series** can be oxidized to **N-oxides.**[10] Uracil, thymine, and guanosine and their derivatives gave ring-cleavage products. N-substituted **aziridines** are presumably oxidized to the corresponding **N-oxides.**[11] This reaction is successfully used in the stereospecific **deamination of N-alkylaziridines** to **olefins.**[11b]

Sulfides can be selectively oxidized to **sulfoxides**[12] or **sulfones**[12a] in excellent yields, even in the presence of amine functions,[12b] or carbon-carbon double and triple bonds.[12c] Some **diaziridinones** have been prepared from **carbodiimides,**[13] and some **ortho esters** from **ketals.**[14]

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