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Published by the
AMERICAN CHEMICAL SOCIETY
1155 16th Street, N.W.
Washington, D. C. 20036

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Published biweekly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second-class postage paid at Washington, D. C., and at additional mailing offices.

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

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JOCEAH 38(19) 3229-3446 (1973)
ISSN 0022-3263

THE JOURNAL OF Organic Chemistry®

VOLUME 38, NUMBER 19 SEPTEMBER 21, 1973

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THE JOURNAL OF Organic Chemistry®

VOLUME 38, NUMBER 19

SEPTEMBER 21, 1973

Steroid Total Synthesis. X.[1] Optically Active Estrone Precursors and Racemic Equilenin Methyl Ether[2]

NOAL COHEN,* BRUCE L. BANNER, JOHN F. BLOUNT, MOUJAU TSAI, AND GABRIEL SAUCY

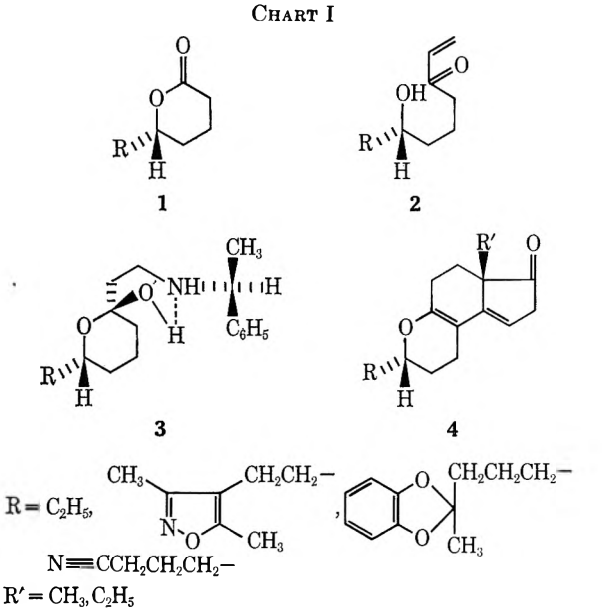
Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received April 11, 1973

A total synthesis of (+)-3-methoxy-1,3,5(10),9(11)-estratetraen-17-one (**27b**, a known precursor of estrone) is described. The key step involves condensation of the optically active Mannich base mixture **14b** with 2-methyl-1,3-cyclopentanedione giving predominantly the desired epimer (1*R*)-(+)-2-(5,6,7,7a-tetrahydro-7a*S*-methyl-1,5-dioxo-4-indanyl)-1-(3-methoxyphenyl)ethanol (**18b**). The latter substance was converted into **27b** *via* the corresponding *p*-bromobenzoate derivative **22b** and the intermediates (*S*)-(+)-7,7a-dihydro-4-(*m*-methoxystyryl)-7a-methyl-1,5(6*H*)-indandione (**24b**) and (*S*)-(+)-7,7a-dihydro-4-[2-(3-methoxyphenyl)ethyl]-7a-methyl-1,5(6*H*)-indandione (**25b**). The Mannich base **14b** was prepared in nine stages starting from *m*-methoxyacetophenone *via* (*R*)-(+)-4-hydroxy-4-(3-methoxyphenyl)butyric acid γ-lactone (**5b**). Configurational assignments were made with the aid of an X-ray analysis of the racemic diketo ester **22a**. In the racemic series, (±)-equilenin 3-methyl ether (**33a**) was obtained in five stages starting from the ketol **18a**.

Previous publications from our laboratories have described several practical approaches to the total synthesis of optically active 19-nor steroids[1,3,4] and related compounds.[5,6] The basic scheme (Chart I) utilizes, initially, the reaction of vinylmagnesium chloride with an appropriately substituted δ-lactone **1** at −50° giving a vinyl ketone **2**. In order to introduce optical activity, the starting lactone may be optically active[5] or, alternatively,[1,3,4,6] the racemic vinyl ketone **2** may be treated with an optically active amine (*e.g.*, α-methylbenzylamine) giving a diastereomeric mixture of Mannich bases. In the latter procedure, the resulting base mixture can be resolved, usually as the oxalic acid salt, giving the desired diasteromer **3** (predominantly the hemiketal form shown). Of crucial importance is the observation[1,3-6] that condensation of a 2-alkylcyclopentane-1,3-dione with the optically active intermediates **2** or **3** (or related 4-hydroxyalkyl vinyl ketone derivatives) occurs with substantial asymmetric induction furnishing predominantly the desired dienol ether **4**, possessing the natural C_{13} configuration. The latter substances can then be transformed efficiently into optically active 19-nor steroids or related B,C,D-tricyclic materials.

CHART I



One logical extension of this synthetic scheme would be its application to the total synthesis of the aromatic steroidal hormones estrone and equilenin in optically active form.[7] The modifications required to achieve this end are delineated in Scheme I.[8] We envisioned

(1) Part IX: N. Cohen, B. Banner, R. Mueller, R. Yang, M. Rosenberger, and G. Saucy, *J. Org. Chem.*, **37**, 3385 (1972).

(2) Presented in part at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972, Abstract No. ORGN 6.

(3) Part VI: J. W. Scott, R. Borer, and G. Saucy, *J. Org. Chem.*, **37**, 1659 (1972).

(4) Part VIII: M. Rosenberger, A. J. Duggan, R. Borer, R. Müller, and G. Saucy, *Helv. Chim. Acta*, **55**, 2663 (1972).

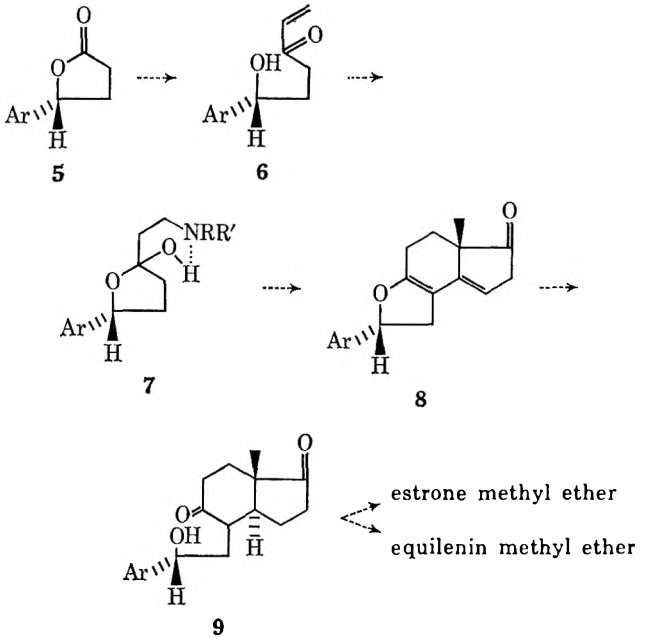
(5) Part II: G. Saucy and R. Borer, *Helv. Chim. Acta*, **54**, 2121 (1971).

(6) Part III: G. Saucy and R. Borer, *Helv. Chim. Acta*, **54**, 2517 (1971).

(7) For other asymmetric total syntheses of estrone or estrone intermediates see (a) R. Bucourt, L. Nédélec, J.-C. Gasc, and J. Weill-Raynal, *Bull. Soc. Chim. Fr.*, 561 (1967); (b) C. Rufer, E. Schröder, and H. Gibian, *Justus Liebigs Ann. Chem.*, **701**, 206 (1967); (c) R. Bucourt, M. Vignau, and J. Weill-Raynal, *C. R. Acad. Sci., Ser. C*, **265**, 834 (1967); (d) U. Eder, G. Sauer, and R. Wiechert, *Angew. Chem.*, **83**, 492 (1971).

(8) Throughout this paper Ar = *m*-methoxyphenyl. Although absolute configurations are shown, racemic modifications are often referred to and are denoted as the **a** series. The **b** and **c** series refer to optically active compounds of the absolute configurations shown.

SCHEME I



the reaction of γ-lactone **5** with vinylmagnesium chloride, giving the vinyl ketone **6**, which either directly or *via* Mannich base **7** hopefully would afford the dienol ether **8** upon condensation with 2-methylcyclopentane-1,3-dione. We considered diene **8** a highly desirable intermediate not only because its formation should proceed with a high degree of asymmetric induction, but also since its catalytic hydrogenation should give mainly the desired 14α stereochemistry by analogy with the course of hydrogenation of the homologous dienol ethers **4** from the previous work.[1,3-6] After hydration of the hydrogenation product (an enol ether), the ketol **9** would be produced, which hopefully could be converted to either estrone methyl ether or equilenin methyl ether by acid-catalyzed cyclization with appropriate manipulation of the benzylic hydroxyl function.

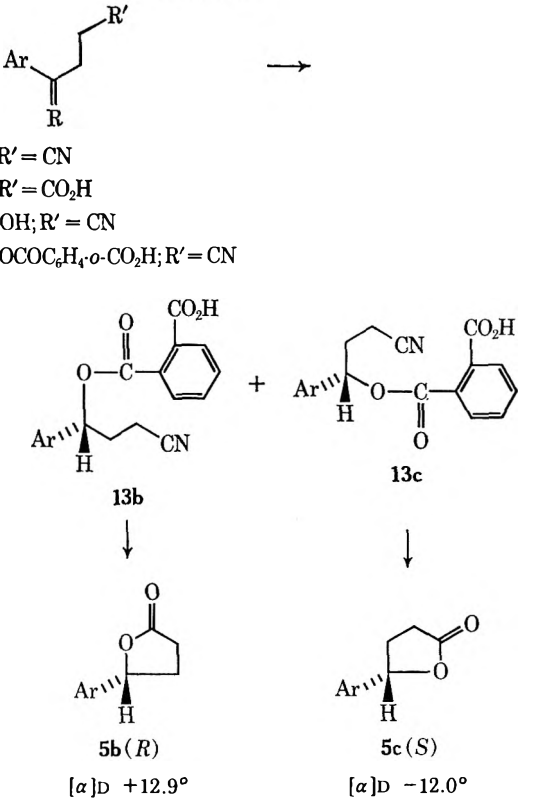
Results and Discussion

The synthesis of the required starting lactone **5** is shown in Scheme II. Commercially available *m*-methoxyacetophenone was converted by standard procedures into the known substances nitrile **10**[9] and acid **11**.[10] Reduction of **11** with sodium borohydride followed by acidification gave the racemic lactone **5a** in 90% yield.

In order to produce optically active materials, we chose the scheme in which an optically active lactone is used as a starting point[5] rather than that involving resolution of a suitable Mannich base.[1,3,4,6] This decision was based primarily on the ready availability of the hydroxy nitrile **12a**, an intermediate which seemed ideally suited for optical resolution at an early stage in the synthesis. This material was prepared in 94% yield by sodium borohydride reduction of **10**.

Resolution of **12a** *via* the acid phthalate derivative **13a** was accomplished readily using (*R*)-(+)-α-methylbenzylamine, which afforded the half ester **13b** in 40% yield. By the use of (*S*)-(−)-α-methylbenzylamine, the enantiometric half ester **13c** was obtained. Basic hydrolysis of these phthalates followed by acidification furnished the (*R*)-(+)-lactone **5b** (89% yield) and (*S*)-(−)-lactone **5c** (84% yield), respectively. It should be noted that, at this point, the absolute configurations of these materials were unknown. Fortuitously, we chose the positively rotating lactone for further transformations which ultimately led to products having the desired natural configuration (see below).

SCHEME II



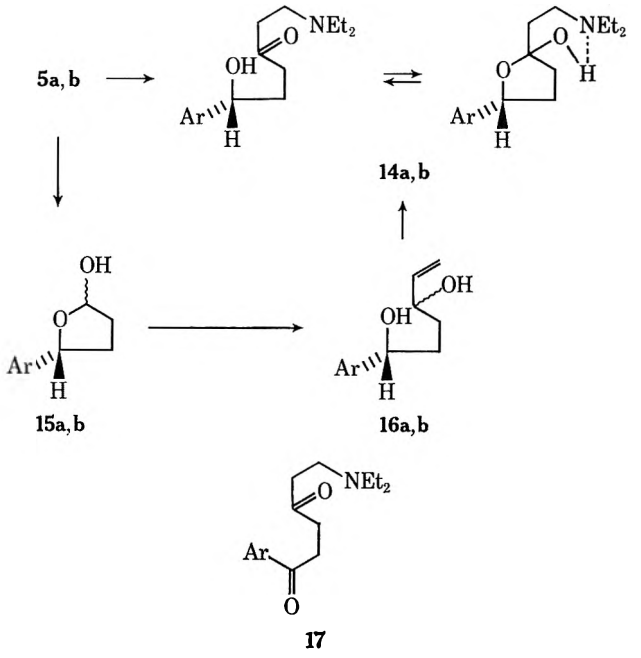
Having the required γ-lactones in hand, we next turned our attention to their conversion into the vinyl ketones **6**. In model studies, the racemic lactone **5a** was treated with vinylmagnesium chloride in tetrahydrofuran at −50°[5] and the resultant crude product was treated directly with diethylamine. This produced the desired Mannich base **14a** (Scheme III) (mixture of keto and hemiketal forms), but in only 11% yield (in striking contrast to the usual 80% yield of the bases derived by the same sequence from δ-lactones[1,3-6]). The neutral fraction isolated from this reaction appeared to consist mainly of divinyl diol resulting from further reaction of the initially formed vinyl ketone with the Grignard reagent.[11]

A possible explanation for the differing behavior of γ- and δ-lactones toward vinylmagnesium chloride involves the nature of the initial products formed in the reaction. The vinyl ketone formed in the δ-lactone case apparently exists under the reaction conditions predominantly in the cyclic form ii, protected from further attack by Grignard reagent. On the other

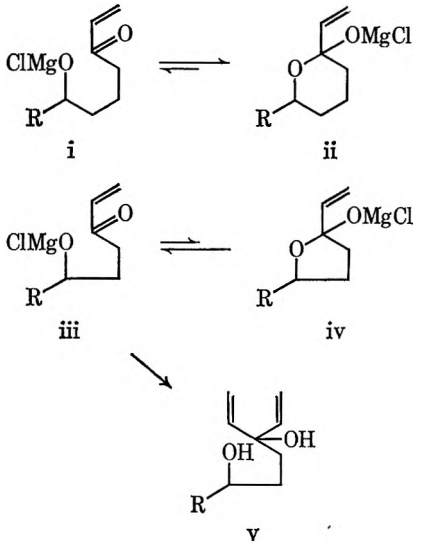
(9) E. B. Knott, *J. Chem. Soc.*, 1190 (1947).
(10) H. W. Thompson, *J. Chem. Soc.*, 2310 (1932).

(11) The reaction of γ-butyrolactone with alkyl Grignard reagents at −70° has previously been reported to give mainly 1,4-diols.[12] On the other hand, the preparation of α,β-ethynyl ketones by reaction of γ-butyrolactones with phenylethynyllithium at −70° has been described recently.[13]
(12) V. N. Belov and Y. I. Tarnopol'skii, *Zh. Org. Khim.*, **1**, 634 (1965), and references cited therein.
(13) H. Ogura, H. Takahashi, and T. Itoh, *J. Org. Chem.*, **37**, 72 (1972).

SCHEME III



hand, the corresponding vinyl ketone derived from the γ-lactone must exist to a great extent in the open form iii, rendering it susceptible to further attack by Grignard reagent and giving rise to the useless divinyl diol v.

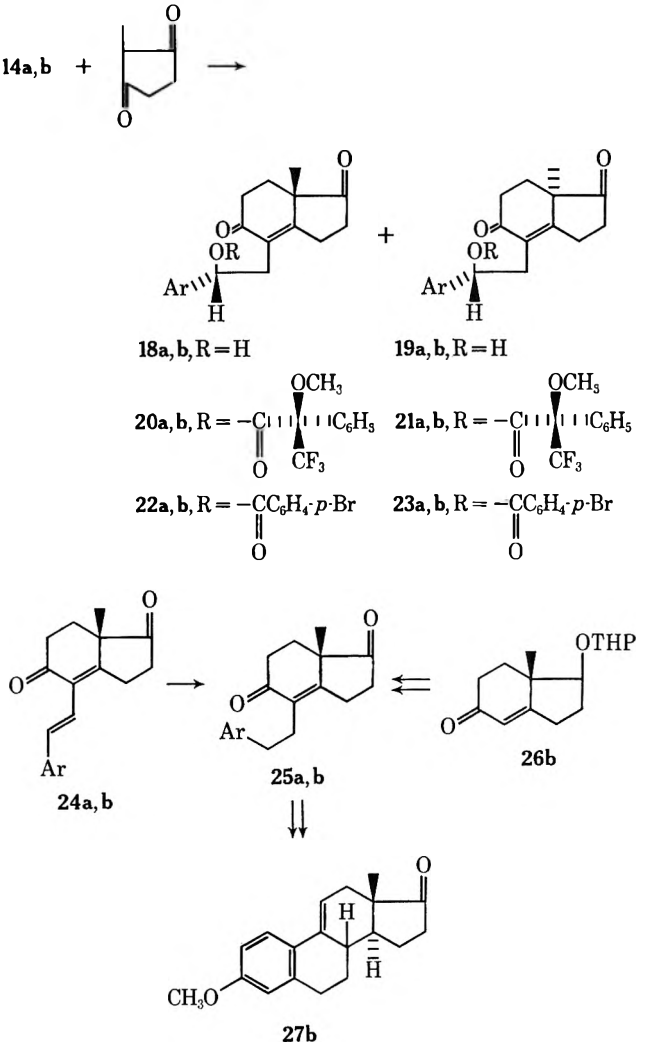


In order to circumvent the difficulty inherent in treating lactone **5** directly with vinylmagnesium chloride, an alternative sequence[5] was employed. Reduction of **5a** with diisobutylaluminum hydride, in toluene, at −70° gave the crystalline lactol **15a** in quantitative yield. Treatment of the latter compound with vinylmagnesium chloride in tetrahydrofuran furnished diol **16a** again in quantitative yield. Oxidation of **16a** with activated manganese dioxide,[14a,b] in benzene, in the presence of diethylamine[5] afforded a mixture of amines in 60% yield, consisting mainly of the desired Mannich base **14a**. By control of the reaction conditions, it was possible to keep the amount of undesired acetophenone **17** formed at trace levels. Using the same sequence of reactions, the (+)-lactone **5b** was converted into the optically active base mixture **14b** in yields comparable to those observed in the racemic series.

The ability to selectively oxidize an allylic alcohol in the presence of a benzylic alcohol with manganese dioxide is, to our knowledge, unprecedented and may find further application in synthesis. Our results are in agreement with those of Gritter and Wallace,[14b] who reported that allyl alcohol is more readily oxidized than benzyl alcohol and suggested a steric effect to be responsible for the rate difference. Similarly, in the case of diol **16**, steric factors are most likely responsible for the difference in rate of oxidation of the two hydroxyl functions.

Condensation of the racemic Mannich base **14a** with 2-methyl-1,3-cyclopentanedione (Scheme IV) in

SCHEME IV



refluxing toluene–acetic acid[15] for 1 hr unexpectedly produced none of the desired dienol ether **8a**. Instead, a mixture of ketols was produced from which the major

(14) (a) M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N. Y., 1967, pp 637–643; Vol. II, 1969, pp 257–263; Vol. III, 1972, pp 191–194; and references cited therein. (b) R. J. Gritter and T. J. Wallace, *J. Org. Chem.*, **24**, 1051 (1959). These authors point out that the rate and specificity of manganese dioxide oxidations is dependent on several factors, one of which is the manner in which the oxidizing agent is prepared. A description of the preparation of the manganese dioxide used for the oxidation of **16** to **14** is included in the Experimental Section.[37]

(15) G. Saucy, R. Borer, and A. Fürst, *Helv. Chim. Acta*, **54**, 2034 (1971).

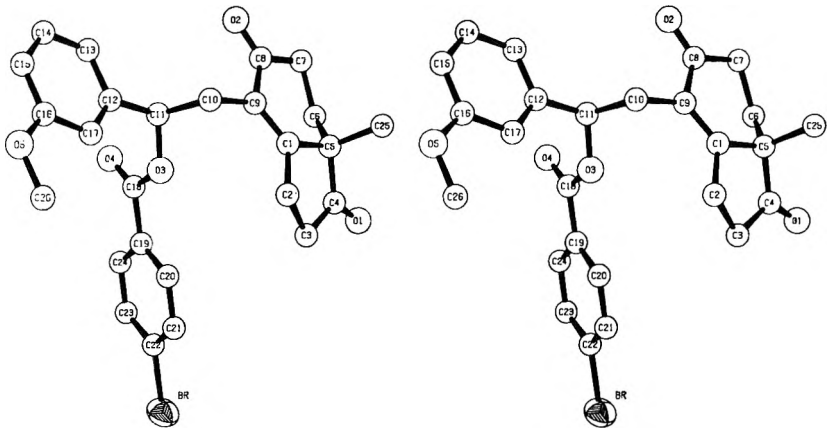


Figure 1.—Stereoview of **22a**.

epimer **18a** was isolated in 50% yield by crystallization. The relative configuration of this material was determined by an X-ray analysis of the corresponding *p*-bromobenzoate derivative **22a** (Figure 1).

Several unsuccessful experiments were carried out in an effort to cyclize **18a** to **8**. Heating in the presence of *p*-toluenesulfonic acid gave the diene **24a**. Treatment of **18a** with acetic anhydride led only to acetylation while exposure to dicyclohexylcarbodiimide in pyridine[16] led to recovered starting material.

The failure to isolate dienol ether **8** is probably due to strain inherent in this tricyclic fused dihydrofuran system (relative to the homologous dihydropyrans **4** isolated previously), making the hydroxy enedione form preferred by virtue of the relative product stabilities. Although we were unable to overcome this second deviation from our original plan, we nonetheless were encouraged by the observation that reaction of **14a** with 2-methyl-1,3-cyclopentanedione appeared to be quite stereoselective (substantially one ketol isomer produced). We felt that the optically active Mannich base **14b** when treated similarly should result in ketol **18b** with substantial asymmetric induction and hopefully (if the stereochemistry at the benzylic center had been properly chosen), affording the required 13β stereochemistry (steroid numbering).[17]

Condensation of the optically active base **14b** with 2-methyl-1,3-cyclopentanedione in refluxing toluene–acetic acid[15] for 1 hr gave a mixture of epimeric ketols **18b** and **19b** in 50–60% yield which, although noncrystalline, could be easily freed of other impurities by column chromatography. This mixture, without separation, was then dehydrated with *p*-toluenesulfonic acid and the disubstituted double bond in the intermediate diene **24** was selectively hydrogenated over palladium on carbon. The resultant enedione **25**,[7d,18] although optically impure, showed a specific rotation in the region of +150°. This result was encouraging, since it indicated that substantial asymmetric induction had taken place in the condensation of the optically active Mannich base **14b** with methylcyclopentanedione. Furthermore, the positive direction of the rotation signified that the preponderant epimer formed in this reaction was the desired **18b** having the natural, *S* configuration at the newly formed ring fusion center.[19,20] It should be noted that the dehydration–hydrogenation sequence was employed since efforts to convert the racemic ketol **18a** directly to tetracyclic materials were unrewarding.

It was of interest to determine the enantiomeric purity of the benzylic center in our intermediates, since we had no assurance that our original optical resolution had been successful or, assuming complete resolution, that racemization of this center had been avoided in the sequence leading from **5b** to **18b** and **19b**. To this end, we employed the nmr method of Mosher and coworkers.[21] Thus, when the mixture of **18b** and **19b** was treated with the acid chloride derived from (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA), an ester mixture (**20b**, **21b**) was produced which showed essentially a single resonance in the ^{19}F nmr spectrum (δ 7.38, downfield from TFA as an external standard) indicating that the benzylic center was enantiomerically pure. On the other hand, when the racemic ketol **18a** was esterified with this reagent, the ester produced exhibited two resonance peaks of approximately equal intensity (δ 7.38, 7.00) in the ^{19}F spectrum.[22]

Examination of the ^{1}H spectra of the esters **20a** and **20b**, **21b** yielded information regarding not only the enantiomeric purity but also the absolute configuration of the benzylic center. Thus, the resonance due to the aromatic methoxyl group in the ester derived from the racemic ketol occurred as two approximately equal peaks at δ 3.78 and 3.74, whereas the spectra of the optically active ester showed only the δ 3.78

(16) This reagent has been used for the dehydration of hydroxy acids to strained lactones; *cf.* R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958); W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger, and W. M. Hubbard, *J. Amer. Chem. Soc.*, **83**, 606 (1961); J. A. Marshall and N. Cohen, *J. Org. Chem.*, **30**, 3475 (1965).

(17) The mechanism of the key asymmetric annelation producing mainly the dienol ethers **4** has been discussed previously.[6] We feel that a similar mechanism is operable in the reaction between **14** and 2-methyl-1,3-cyclopentanedione leading to a preponderance of ketol **18** over the epimer **19**.

(18) G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, 5072 (1963).

(19) W. Aeklin, V. Prelog, and A. P. Prieto, *Helv. Chim. Acta*, **41**, 1416 (1958).

(20) Z. G. Hajos, D. R. Parrish, and E. P. Oliveto, *Tetrahedron*, **24**, 2039 (1968).

(21) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).

(22) It should be noted that the MTPA ester produced in the optically active series is epimeric at C_{13} (steroid numbering). This factor should have no effect on the analysis of enantiomeric purity at C_6, however, because of the distance separating the two asymmetric centers.

resonance peak. On the basis of the configurational correlation model proposed recently for MTPA derivatives,[23] it would be predicted that our optically active ketols **18b** and **19b**, the MTPA ester mixture derived from which exhibited the relatively lower field aromatic methoxy resonance, have the *R* configuration at the benzylic center. This assignment was confirmed by the ensuing transformations (see below).

Our next problem involved the synthesis of enedione **25b** in optically pure form. To accomplish this it was necessary to free the required ketol **18b** from its isomer **19b**. In contrast to the behavior in the racemic series, this mixture could not be induced to crystallize. When the mixture was converted to the *p*-bromobenzoate derivative, however, a crystalline product was obtained, recrystallization of which led, in 46% yield, to the desired major isomer **22b** in pure form. This material was spectrally and chromatographically identical with the racemic modification on which the X-ray analysis had been carried out. The minor ester **23b** was never isolated in pure form.

Since both the absolute configuration at C_{13} (steroid numbering) and the relative configuration of the two asymmetric centers in ester **22b** are known, it follows that the absolute configuration of the benzylic center must be *R* as predicted above. Thus, the absolute configuration of the positively rotating lactone **5b** from which **22b** is derived must be *R* also.

Treatment of **22b** with *p*-toluenesulfonic acid in refluxing toluene gave the crystalline diene **24b** (81% yield) which on selective hydrogenation over palladium on carbon furnished optically pure enedione **25b**, now showing $[\alpha]_D$ +195°, in 98% yield. From this value and the rotation obtained for **25b** when no separation of ketols **18b** and **19b** was carried out (+153°), it was possible to estimate that the ratio of **18b** to **19b** in the original mixture was approximately 8:1.

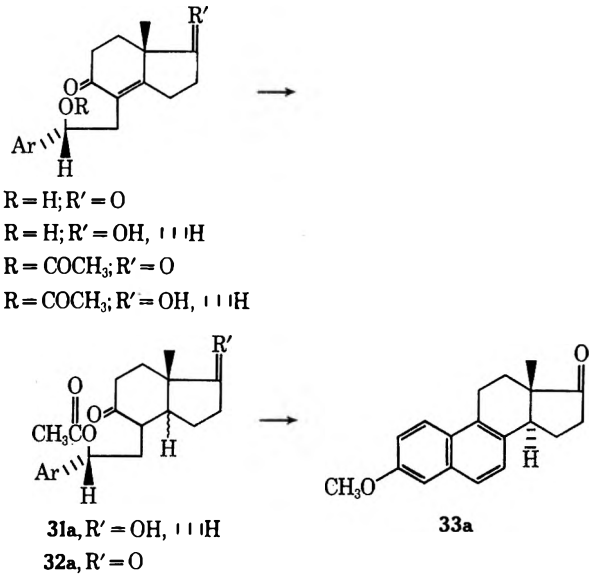
In order to verify the optical purity of enedione **25b** this material was synthesized by an alternative route starting from a substance of known optical purity. Thus, the (+)-tetrahydropyranyl ether **26b**[20] was alkylated with *m*-methoxyphenethyl tosylate using the procedure of Whitehurst and coworkers.[24] Acid hydrolysis of the product followed by oxidation with Jones reagent[25] gave **25b**. The optical rotations for the enedione samples produced by the two routes were in excellent agreement. While this work was in progress, an alternative asymmetric synthesis of **25b** was disclosed.[7d]

Enedione **25b** (produced from **22b**) was converted to (+)-3-methoxy-1,3,5(10),9(11)-estratetraen-17-one (**27b**) using known procedures.[18] The properties of **27b** obtained in this way were in excellent agreement with those reported.[26,27] The final steps leading to estrone have been described previously.[18]

(23) J. A. Dale and H. S. Mosher, *J. Amer. Chem. Soc.*, **95**, 512 (1973).
(24) D. J. Crispin, A. E. Vanstone, and J. S. Whitehurst, *J. Chem. Soc. C*, 10 (1970).
(25) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(26) K. Tsuda, S. Nozoe, and Y. Okada, *Chem. Pharm. Bull.*, **11**, 1271 (1963).
(27) K. Tsuda, E. Ohki, and S. Nazoe, *J. Org. Chem.*, **28**, 786 (1963).

A synthesis of racemic equilenin methyl ether starting from the ketol **18a** is shown in Scheme V. In order to carry out this transformation, a procedure was required which would allow selective catalytic hydrogenation of the enone double bond whicle preserving the benzylic hydroxyl function. Our initial studies were performed on the diol **28a**,[28] derived from **18a** by selective borohydride reduction.[29] Unfortunately, when **28a** was hydrogenated over palladium catalysts, both double-bond reduction and benzylic alcohol hydrogenolysis were found to occur simultaneously. In addition, substantial amounts of materials in which the carbonyl group had been lost by hydrogenolysis were obtained.

SCHEME V



A somewhat more successful approach involves prior acetylation of the hydroxyl group giving the diketo acetate **29a**. Selective reduction[29] with sodium borohydride then afforded the corresponding 17β-ol **30a**[28] in essentially quantitative overall yield from **18a**. After many failures with other catalysts, it was found that hydrogenation of **30a** over palladium on barium sulfate yielded the desired keto acetate **31a** (mixture of isomers) in 25% yield. Oxidation[25] of the latter material followed by cyclization–aromatization of the resulting diketo acetate **32a** by treatment first with methanolic hydrochloric acid[18] and then with *p*-toluenesulfonic acid in refluxing benzene gave racemic equilenin methyl ether (**33a**)[18,30-32] in 42% yield. The material thus produced was spectrally and chromatographically identical with the ether obtained by methylation of natural equilenin.[33]

(28) Hydrogenation of **18a** or **29a** was not attempted since it is known that, in such systems, the 17 ketone gives rise to more of the undesired cis-fused hydrindanone than the corresponding 17β-hydroxy compound.[18]
(29) J. N. Gardner, B. A. Anderson, and E. P. Oliveto, *J. Org. Chem.*, **34**, 107 (1969).
(30) A. Horeau, E. Lorthioy, and J. P. Guetté, *C. R. Acad. Sci., Ser. C*, **269**, 558 (1969).
(31) W. S. Johnson, J. W. Petersen, and C. D. Gutsche, *J. Amer. Chem. Soc.*, **69**, 2942 (1947).
(32) R. P. Stein, G. C. Buzby, Jr., and H. Smith, *Tetrahedron*, **26**, 1917 (1970).
(33) W. E. Bachmann, W. Cole, and A. L. Wilds, *J. Amer. Chem. Soc.*, **62**, 824 (1940).

Experimental Section[34]

3-(3-Methoxybenzoyl)propionitrile (10).—3-Dimethylamino-*m*-methoxypropiophenone hydrochloride was prepared in 80% yield from *m*-methoxyacetophenone using the procedure of Nobles and Burckhalter.[35] White solid, mp 166–168°, was obtained (lit.[35] mp 168°). This material was converted into keto nitrile **10** in 58% yield by the method described by Knott.[9] Pale yellow solid, mp 52–53.5°, was obtained after recrystallization from methanol (lit.[9] mp 54°).

3-(3-Methoxybenzoyl)propionic Acid (11). **A.**—A 37.5-g (0.78 mol) sample of 50% sodium hydride–mineral oil dispersion was washed several times with hexane in a stream of nitrogen. A 610-ml portion of redistilled dimethyl carbonate was then added and the mixture was stirred in an oil bath at 90° while 111 g (0.74 mol) of *m*-methoxyacetophenone was added dropwise. As soon as the reaction began, the oil bath was removed and the addition of the ketone was continued over 40 min. The resulting brown solution was heated at reflux for 1 hr, then cooled in an ice bath and neutralized with 70 ml of glacial acetic acid. The resulting mixture was treated with 500 ml of ice water and worked up with ether (the organic extracts were additionally washed with aqueous sodium bicarbonate solution). Removal of ether and excess dimethyl carbonate left 163 g of orange, oily methyl *m*-methoxybenzoylacetate which was sufficiently pure for further use. A sample was distilled, bp 103–108° (0.2 mm) [lit.[36] bp 140–148° (0.8–1.4 mm)].

A 35.6-g (0.74 mol) sample of 50% sodium hydride–mineral oil dispersion was washed several times with hexane and then suspended in 450 ml of dry tetrahydrofuran. The resulting mixture was stirred while 160 g (0.74 mol) of crude methyl *m*-methoxybenzoylacetate was added dropwise. After heating at reflux for 1 hr, the reaction mixture was cooled in an ice bath and 113.5 g (0.74 mol) of methyl bromoacetate in 40 ml of dry tetrahydrofuran was added dropwise. After the addition was complete, the reaction mixture was stirred and heated at reflux for 1 hr, then cooled and the precipitated sodium bromide was filtered with suction. The filtrate was concentrated at reduced pressure and the residue was treated with 300 ml of ether and 8 ml of glacial acetic acid. Work-up with ether gave 206 g of crude product from which some mineral oil was decanted. Distillation afforded 163.5 g (79%) of dimethyl *m*-methoxybenzoylsuccinate as a viscous yellow oil, bp 152–156° (0.1 mm) [lit.[36] bp 161–162° (0.35 mm)].

A mixture of 163.5 g (0.586 mol) of this keto diester and 670 ml of concentrated hydrochloric acid was stirred at reflux for 20 hr. The mixture was cooled, diluted with 300 ml of water, and extracted with methylene chloride. The methylene chloride layer was in turn extracted with 1 l. of 10% aqueous sodium hydroxide and discarded. The alkaline solution was then chilled in an ice bath and acidified with concentrated hydrochloric acid. The precipitated product was filtered with suction, washed with water, and dried. Recrystallization from a mixture of 400 ml of benzene and 50 ml of hexane gave 59.4 g of first crop as tan solid, mp 104–107°, and 19.1 g of second crop, mp 105–107° (lit.[10] mp 108°). The total yield of **11** was 69.5%.

B.—A mixture of 39.9 g (0.211 mol) of keto nitrile **10** and 250 ml of 10% aqueous sodium hydroxide was stirred at reflux for 4 hr. The resulting red solution was cooled and extracted twice with ether and the ether extracts were discarded. The aqueous alkaline solution was acidified with 50 ml of concentrated HCl and worked up with methylene chloride. The solid residue was recrystallized from benzene, giving 33.5 g (76.2%) of off-white solid, mp 108–109°.

(±)-4-Hydroxy-4-(3-methoxyphenyl)butyric Acid γ-Lactone (5a).—A solution of 33.5 g (0.161 mol) of keto acid **11** in 400 ml of 10% aqueous sodium hydroxide was stirred while a solution of 12.1 g (0.32 mol) of sodium borohydride in 60 ml of water was added dropwise. The resulting solution was stirred at room temperature for 4 hr, then cooled in an ice bath and cautiously treated dropwise with 240 ml of concentrated hydrochloric acid. After stirring at 40–50° for 45 min the reaction mixture was cooled and worked up with ether (the ether extracts were additionally washed with two portions of saturated aqueous sodium bicarbonate), giving 30 g of viscous oily lactone. Distillation afforded 27.85 g (90%) of colorless oil, bp 133–140° (0.2 mm). A sample was evaporatively redistilled giving an analytical specimen, ir ($CHCl_3$) 1780 cm^{-1} (lactone C=O).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.78; H, 6.31. Found: C, 69.00; H, 6.34.

(±)-4-Hydroxy-4-(3-methoxyphenyl)butyronitrile (12a).—A slurry of 14.9 g (0.079 mol) of the keto nitrile **10** in 120 ml of absolute ethanol was stirred in an ice–salt bath at −5 to 0° while a solution of 1.5 g (0.04 mol) of sodium borohydride in 100 ml of absolute ethanol was added dropwise over a 30-min period. The reaction mixture was gradually allowed to warm to room temperature as it was stirred for 1.25 hr, then neutralized with 1 *N* aqueous HCl and worked up with ether. There was obtained 14.2 g (94.3%) of the crude hydroxy nitrile **12a** as a colorless liquid which was sufficiently pure for further use.

A sample from a similar run was chromatographed on silica gel (50 parts, eluted with 9:1 benzene–ether) and evaporatively distilled to give the analytical sample as a pale yellow liquid, bp 130–175° (bath temperature) (0.07 mm). This material showed a single spot on tlc analysis; ir ($CHCl_3$) 3475, 3600 (OH), 2250 (C≡N), 1590, 1600 cm^{-1} (anisole); mass spectrum *m/e* 191 (M^+).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.83; H, 6.80; N, 7.16.

(±)-[3-Cyano-1-(3-methoxyphenyl)]-1-propyl Hemiphthalate (13a).—A solution of 56.1 g (0.294 mol) of crude hydroxy nitrile **12a**, 44.4 g (0.3 mol) of phthalic anhydride, and 160 ml of anhydrous pyridine was heated at 100° for 5 hr. The reaction mixture was cooled and poured into a mixture of ice and 3 *N* aqueous hydrochloric acid and the resulting acidic aqueous solution was extracted three times with ether. The ether extracts were combined and extracted with 10% aqueous sodium carbonate solution, then discarded. The alkaline extracts were combined, washed with ether (discarded), then carefully acidified with 10% aqueous HCl and extracted with chloroform. There was obtained 93.6 g (93.8%) of hemiphthalate **13a** as a brown oil which was used without purification. A sample from a similar experiment showed the following spectral data: ir ($CHCl_3$) 3400–3050 (broad H-bonded OH), 2250 (C≡N), 1740 (ester C=O), 1710 (acid C=O), 1605, 1595 cm^{-1} (anisole); mass spectrum *m/e* 339 (M^+).

(*R*)-(−)-3-Cyano-1-(3-methoxyphenyl)-1-propyl Hemiphthalate (13b) (*R*)-(+)-α-Methylbenzylamine Salt.—To a solution of 93.6 g (0.276 mol) of crude hemiphthalate **13a** in 200 ml of acetonitrile was added 35 g (0.29 mol) of (*R*)-(+)-α-methylbenzylamine in 20 ml of acetonitrile. The mixture was heated on the steam bath for 5 min, and then allowed to stand for 2 days at room temperature. The white solid obtained was recrystallized twice from acetonitrile, giving 25.3 g (39.8%) of pure salt as a colorless solid, mp 124.5–126°, $[\alpha]^{25}D$ −51.08° (*c* 1, EtOH).

The analytical specimen showed mp 122–123.5°; $[\alpha]^{25}D$ −51.57° (c 1, EtOH); nmr ($CDCl_3$) δ 8.37 (m, 3, NH_3^+), 7.23 (m, 13, aromatic), 5.85 (m, 1, HCO), 4.16 (m, 1, PhCH), 3.72 (s, 3, OCH_3), 2.19 (m, 4, CH_2CH_2CN), 1.38 ppm (d, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{19}H_{17}NO_5 \cdot C_8H_{11}N$: C, 70.42; H, 6.13; N, 6.08. Found: C, 70.22; H, 5.96; N, 5.86.

(*S*)-(+)-[3-Cyano-1-(3-methoxyphenyl)]-1-propyl Hemiphthalate (13c) (*S*)-(−)-α-Methylbenzylamine Salt.—A resolution of 187.6 g (0.556 mol) of acid phthalate **13a** was carried out with (*R*)-(+)-α-methylbenzylamine as described in the preceding

(34) Unless otherwise noted, reaction products were isolated by addition of brine and extraction with the specified solvent. Organic solutions were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under water aspirator pressure at 40–50° on a rotary evaporator. The crude reaction products were then dried under high vacuum to constant weight. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. All reactions except hydrogenations were carried out under an atmosphere of nitrogen. Column chromatography was performed using Merck (Darmstadt) silica gel, 0.05–0.2 mm. Thin layer chromatography was performed using Brinkmann silica gel G plates with uv indicator. Unless otherwise noted plates were developed with 1:1 benzene–ethyl acetate. Spots were detected with uv light, iodine vapor, or *p*-toluenesulfonic acid spray followed by heating. Varian A-60 and HA-100 or Jeolco C-60H spectrometers were used to obtain the pmr spectra. Chemical shifts are reported relative to TMS. Infrared spectra were recorded on a Beckman IR-9 spectrophotometer. The uv spectra were recorded on a Cary Model 14 M spectrophotometer. Low-resolution mass spectra were obtained on CEC 21-110 or JMS-01SG instruments. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Tetrahydrofuran and pyridine were slurried over Woelm grade I neutral alumina just prior to use.

(35) W. L. Nobles and J. H. Burckhalter, *J. Amer. Pharm. Ass. Sci. Ed.*, **47**, 77 (1958).

(36) J. J. Korst, J. D. Johnston, K. Butler, E. J. Bianco, L. H. Conover, and R. B. Woodward, *J. Amer. Chem. Soc.*, **90**, 439 (1968).

experiment. The mother liquor and washes after removal of the first crop of *R,R* salt were combined and concentrated *in vacuo*, giving a brown, oily residue. This material was treated with aqueous 3 *N* HCl and extracted with ether, affording 114 g (0.337 mol) of hemiphthalate as a brown oil. After dissolution in 200 ml of acetonitrile this material was treated with a solution of 41 g (0.338 mol) of (*S*)-(−)-α-methylbenzylamine in 50 ml of acetonitrile. The mixture was heated on the steam bath for 15 min and then allowed to stand for 2 days at room temperature. The white solid obtained was recrystallized twice from acetonitrile, giving 36.3 g (28.4%) of the pure *S,S* salt as a white solid, mp 132–133°, $[\alpha]^{25}D$ +55.75° (*c* 1, EtOH). The nmr spectrum was essentially identical with that of the *R,R* salt.

Anal. Calcd for $C_{19}H_{17}NO_5 \cdot C_8H_{11}N$: C, 70.42; H, 6.13; N, 6.08. Found: C, 70.64; H, 6.27; N, 6.08.

(*S*)-(−)-4-Hydroxy-4-(3-methoxyphenyl)butyric Acid γ-Lactone (5c).—A 10-g (0.022 mol) sample of the *S,S* salt from the preceding experiment was treated with 3 *N* aqueous HCl and the resultant acid was isolated by ether extraction, giving the hemiphthalate **13c** as a colorless oil, $[\alpha]^{25}D$ +21.77° (*c* 1, EtOH). This material was treated with 160 ml of 10% aqueous NaOH and heated at reflux with stirring for 5 hr. The reaction mixture was cooled, washed once with ether, acidified with 3 *N* aqueous HCl, and stirred for 1.75 hr at room temperature. The reaction mixture was then saturated with sodium chloride and the product was isolated with ether. (The combined organic extracts were additionally washed with saturated aqueous sodium bicarbonate solution.). The residual colorless oil was evaporatively distilled, giving 3.5 g (83.8%) of the lactone **5c** as a colorless liquid, bp 170–185° (bath temperature) (0.1 mm), $[\alpha]^{25}D$ −12.05° (*c* 1, EtOH). Tlc analysis showed a single spot, R_f 0.4; ir ($CHCl_3$) 1780 (γ-lactone C=O), 1605, 1590 cm^{-1} (anisole); mass spectrum *m/e* 192 (M^+). The spectra were essentially identical with those of the racemic form **5a** and the *R* isomer **5b**.

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.45; H, 6.34.

(*R*)-(+)-4-Hydroxy-4-(3-methoxyphenyl)butyric Acid γ-Lactone (5b).—A 36.7-g (0.08 mol) sample of the (*R*)-(+)-α-methylbenzylamine salt of the *R* hemiphthalate **13b** was converted into the acid as described in the previous experiment, giving **13b** as a colorless oil. A sample from a similar experiment showed $[\alpha]^{25}D$ −22.02° (*c* 1, EtOH). This material was hydrolyzed and lactonized as described in the previous experiment, giving 13.6 g (88.8%) of lactone **5b** as a colorless liquid. A sample was evaporatively distilled, giving a colorless liquid, bp 170–180° (bath temperature) (0.1 mm), $[\alpha]^{25}D$ +12.93° (*c* 1, EtOH). The ir, nmr, and mass spectra and the tlc mobility were identical with those of the *S* and *R,S* modifications.

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.44; H, 6.18.

(±)-Mannich Base Mixture 14a. A. From Lactone 5a.—The procedure of Saucy and Borer[5] was employed. A solution of 19.2 g (0.1 mol) of lactone **5a** in 64 ml of dry tetrahydrofuran was cooled to −65° and stirred while 80 ml (0.16 mol) of 2 *M* vinylmagnesium chloride in tetrahydrofuran was added dropwise over 40 min keeping the internal temperature at −50 to −60°. The mixture was stirred for 10 min more at this temperature, decomposed with 10 ml of methanol keeping the temperature near −50°, and poured onto a mixture of 80 g of ice, 6 ml of glacial acetic acid, and 16 g of ammonium chloride. The resulting mixture was extracted three times with ether and the combined extracts were treated with 50 ml of diethylamine and dried over anhydrous magnesium sulfate for 1 hr at room temperature. After filtration, the ether solution was concentrated at reduced pressure, giving 25.2 g of a yellow oil. This material was redissolved in ether and washed three times with 50-ml portions of 1 *N* aqueous hydrochloric acid. The combined acid extracts were washed once with ether and the combined ether solutions were dried over magnesium sulfate and set aside.

The combined acid washes were chilled in an ice bath and made alkaline with 50 ml of 10% aqueous sodium hydroxide. The mixture was worked up with ether, giving 3.22 g (11%) of yellow oily, Mannich base mixture **14a**: ir (film), 3330 (OH), 3180 (broad H-bonded OH), 1710 (ketone C=O, m), 1600 cm^{-1} (anisole); uv max (95% EtOH) 215 nm (ε 8780), 272 (2070), 279 (1900); nmr ($CDCl_3$) δ 7.00 (m, aromatic), 5.19 (t, *J* = 7 Hz, HCO of major component), 4.95 (m, HCO of minor component, approximately 0.33 of major component), 3.76 (s, OCH_3), 1.05 ppm (2 t, $-CH_2CH_3$ of each component); mass spectrum *m/e* 293 (M^+). Tlc analysis (9:1 C_6H_6–Et_3N) showed a single spot, R_f 0.3.

The ether solution containing neutral material which had been set aside was filtered and concentrated at reduced pressure. The residual yellow oil was stirred for 17 hr at room temperature in 100 ml of 2.8 *M* methanolic sodium hydroxide. This solution was concentrated at reduced pressure and worked up with ether, giving 15.4 g of the oily divinyl diol **v** (R = *m*-methoxyphenyl), ir (film) 3450 (OH), 3125 (HC=), 1640 (C=C), 1615 (anisole), 995, 885 cm^{-1} (vinyl).

B. From Diol 16a.—The method of Saucy[5] was employed. A slurry of 660 ml of benzene and 284 g of activated manganese dioxide[37] was stirred with ice-bath cooling while 42 ml of diethylamine was added followed by 28.2 g (0.127 mol) of crude diol **16a**. The ice bath was removed and the reaction mixture was stirred at room temperature for 4.5 hr. The manganese dioxide was filtered with suction and the filter cake was washed thoroughly with methylene chloride. The combined filtrate and washes were concentrated at reduced pressure. The red oily residue was dissolved in ether and the ether solution was extracted three times with 1 *N* aqueous HCl and set aside. The combined acidic, aqueous solutions were basified with 10% potassium hydroxide and worked up with ether, giving 22.4 g (60.3%) of red, oily Mannich base mixture **14a**. The material produced in this manner typically showed the following spectral properties: uv max (95% EtOH) 214 nm (ε 9990), 253 (1210), 271 (1860), 278 (1720), 303 (360); ir (film) 3000–3600 (H-bonded OH), 1710 (C=O), 1680 (shoulder, acetophenone impurity C=O), 1590, 1600 cm^{-1} (anisole). Tlc analysis (9:1 C_6H_6:Et_3N) showed a main spot, R_f 0.3, with a more mobile, minor impurity (acetophenone **17**). The major spot was identical with that of the Mannich base produced in part A.

The ether extracts containing neutral products which had been set aside afforded 6.7 g of oily material which appeared by tlc and spectral analysis to be a mixture of three components, one of which was the starting diol. It was found that longer exposure to MnO_2 led to increased amounts of acetophenone **17** in the product.

Optically Active Mannich Base Mixture 14b.—A 1.98-g (0.0084 mol) sample of crude, optically active diol **16b** was oxidized with 18 g of activated manganese dioxide[37] in 60 ml of benzene and 3 ml of diethylamine using the procedure described for the racemic modification in part B of the preceding experiment. There was obtained 1.7 g (68.8%) of Mannich base **14b** as a red oil which was used without further purification. The ir spectrum and tlc mobility were identical with those of the racemic modification.

(±)-5-(3-Methoxyphenyl)tetrahydrofuran-2-ol (15a).—A solution of 8.82 g (0.046 mol) of lactone **5a** in 60 ml of dry toluene was stirred at −70° while 50 ml of a 25% solution of diisobutylaluminum hydride in toluene (Texas Alkyls Co.) was added dropwise over 10 min. The resulting mixture was stirred at −70° for 1 hr, then cautiously poured into a mixture of 70 g of ice and 18 ml of glacial acetic acid. The toluene layer was separated and work-up with ether was carried out in the usual manner (the organic solution was additionally washed with aqueous sodium bicarbonate solution). This gave 9 g of colorless oil which crystallized on standing. Recrystallization from benzene–hexane gave 6.87 g (77.2%) of white solid, mp 76–78°. An analytical sample was obtained by further recrystallization from benzene–hexane as a colorless solid: mp 76.5–78°; ir ($CHCl_3$) 3450, 3625 (OH), 1600 cm^{-1} (anisole).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.01; H, 7.28. Found: C, 67.74; H, 7.16.

(5*R*)-5-(3-Methoxyphenyl)tetrahydrofuran-2-ol (15b).—A 1.87-g (0.01 mol) sample of (*R*)-(+)-lactone **5b** was reduced proportionately, with diisobutylaluminum hydride using the procedure described in the previous experiment. There was obtained 1.8 g of crude lactol **15b** as a colorless oil. The ir spectrum and tlc mobility were identical with those of the racemic modification. This material was used without purification.

(37) The activated manganese dioxide used in this work was prepared by Dr. D. Andrews of the Technical Development Division, Hoffmann-La Roche Inc., Nutley, N. J. The following procedure is typical. Pyrolusite (10 kg) was added in portions to a solution of 5 l. of concentrated HNO_3 in 20 l. of hot water and the entire mixture was heated at reflux for 30 min. After cooling, the acid solution was siphoned off and the residual manganese dioxide was washed in turn with hot water (3 × 25 l.), 1% aqueous sodium bicarbonate (25 l.), and water (2 × 25 l.) and then dried to constant weight at 100–120° in a circulating air oven. The recovery of MnO_2 was 79%.

(±)-1-(3-Methoxyphenyl)-5-hexene-1,4-diol (16a).—The procedure of Saucy and Borer[6] was employed. A solution of 24.9 g (0.128 mol) of crude lactol **15a** in 135 ml of dry tetrahydrofuran was added dropwise to 210 ml of stirred, 2 *M* vinylmagnesium chloride in tetrahydrofuran with occasional cooling to moderate the exothermic reaction. After the addition was complete, the solution was stirred at room temperature for 3 hr and then poured into 600 ml of ice-cold aqueous ammonium chloride solution and worked up with ether. The residual, pale-yellow, oily diol (28.3 g; 99%) was sufficiently pure for further use. A sample from another identical run was chromatographed on silica gel. The materials from the fractions eluted with 3:2 benzene–ether to pure ether were combined and evaporatively distilled, giving the analytical sample as a viscous, colorless oil, bp 155–163° (bath temperature) (0.2 mm). Tlc analysis showed a single spot, R_f 0.25; ir ($CHCl_3$) 3400, 3600 (OH), 1600 (anisole), 990 cm^{-1} (vinyl).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.23; H, 8.18. Found: C, 70.02; H, 8.32.

(1*R*)-1-(3-Methoxyphenyl)-5-hexene-1,4-diol (16b).—This material was prepared from lactol **15b** in quantitative yield using the procedure described in the preceding experiment for the racemic modification. The crude diol was a viscous, pale-yellow oil which was spectrally and chromatographically identical with the racemic modification and was used without further purification.

(1*R*,*S*)-2-[5,6,7,7a-Tetrahydro-(7a*S*,*R*)-methyl-1,5-dioxo-4-indanyl]-1-(3-methoxyphenyl)ethanol (18a).—The procedure of Saucy, *et al.*,[15] was employed. A mixture of 4 g (0.0137 mol) of crude racemic Mannich base mixture **14a** prepared as described above (MnO_2 method), 1.62 g (0.0145 mol) of 2-methyl-1,3-cyclopentanedione, 15 ml of acetic acid, and 55 ml of toluene was stirred and heated at reflux for 1 hr. After cooling, the resulting solution was diluted with ether and washed three times with water and twice with saturated aqueous sodium bicarbonate. Completion of the usual work-up gave 4.097 g of the mixture of **18a** and **19a** as a red gum. This material was recrystallized from hexane–benzene, giving 2.172 g (50.4%) of tan solid, mp 110–112° (tlc, R_f 0.33). Further recrystallization of a sample gave the analytical specimen of **18a**: mp 113–114°; uv max (95% EtOH) 217 nm (ε 10,800), 251 (9320), 279 (2600); ir ($CHCl_3$) 3500, 3625 (OH), 1750 (cyclopentanone C=O), 1660 (conjugated ketone C=O), 1600 cm^{-1} (anisole); mass spectrum *m/e* 314 (M^+); nmr ($CDCl_3$) δ 1.17 (s, 3, C_{7a} CH_3), 3.76 (s, 3, OCH_3), 4.82 ppm (m, 1, HCO).

Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.58; H, 7.07. Found: C, 72.37; H, 6.81.

The minor epimer **19a** exhibits the same tlc mobility as **18a** and was never isolated in pure form. In another run, the crude product (1.09 g) was chromatographed on 50 g of silica gel. Elution with 49:1 to 4:1 benzene–ether gave fractions containing 0.176 g of impurities which were less polar than the ketols **18a** and **19a**. Spectroscopic investigation of these materials failed to reveal the presence of the diene **8a**. Elution with 1:1 benzene–ether gave 0.801 g (69.7%) of the crystalline mixture of ketols **18a** and **19a**.

Attempted Conversion of Ketol 18a to the Diene 8a.—A solution of 31.4 mg (0.1 mmol) of ketol **18a** and 22 mg (0.106 mmol) of *N*,*N*′-dicyclohexylcarbodiimide[16] in 1 ml of dry pyridine was stirred at room temperature. After 3.25 hr tlc analysis indicated that only the starting materials were present. The solution was then heated at 105–110° for 19 hr. After cooling, work-up with ether gave a quantitative recovery of starting materials (tlc).

Treatment of **18a** with *p*-toluenesulfonic acid in refluxing benzene or with acetic anhydride gave the diene **24a** or the diketo ester **29a**, respectively. These reactions are described in detail below. Again, no trace of the diene **8a** was detected.

(1*R*)-(+)-2-[5,6,7,7a-Tetrahydro-(7a*S*)-methyl-1,5-dioxo-4-indanyl]-1-(3-methoxyphenyl)ethanol (18b) and (1*R*)-2-[5,6,7,7a-Tetrahydro-(7a*R*)-methyl-1,5-dioxo-4-indanyl]-1(3-methoxyphenyl)ethanol (19b).—A mixture of 8.3 g (0.028 mol) of the crude optically active Mannich base **14b**, 3.36 g (0.03 mol) of 2-methyl-1,3-cyclopentanedione, 30 ml of glacial acetic acid, and 100 ml of toluene was stirred and heated at reflux for 1 hr. The reaction mixture was cooled and worked up with ether as described for the racemic series above, giving 8.2 g of crude, red, oily product. This material was chromatographed on 400 g of silica gel. The fractions eluted with 1:1 benzene–ether and ether afforded 5.5 g (62%) of the mixture of ketols **18b** and **19b** with the former predominating, as an orange oil: $[\alpha]^{25}D$ +117.59° (c 1, EtOH); this material was essentially homogeneous on tlc analysis; uv max (95% EtOH) 219 nm (ε 10,410), 252 (8675), 279 (2820); ir ($CHCl_3$) 3450, 3600 (OH), 1750 (cyclopentanone C=O), 1655 (conjugated ketone C=O), 1590, 1600 cm^{-1} (anisole); mass spectrum *m/e* 314 (M^+); nmr ($CDCl_3$) δ 4.82 (m, 1, HCO), 3.72 (s, 3, OCH_3), 1.13 ppm (s, 3, C_{7a} CH_3).

(1*R*)-2-[5,6,7,7a-Tetrahydro-(7a*S*)-methyl-1,5-dioxo-4-indanyl]-1-(3-methoxyphenyl)ethyl (*R*)-α-Methoxy-α-trifluoromethylphenylacetate (20b) and (1*R*)-2-[5,6,7,7a-Tetrahydro-(7a*R*)-methyl-1,5-dioxo-4-indanyl]-1-(3-methoxyphenyl)ethyl (*R*)-α-Methoxy-α-trifluoromethylphenylacetate (21b).—The procedure of Mosher *et al.*,[21] was employed. A mixture of 105.6 mg (0.336 mmol) of the optically active hydroxy enedione mixture **18b** and **19b**, 92.3 mg (0.365 mmol) of the acid chloride[21] derived from (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (Aldrich), 50 drops of carbon tetrachloride, and 25 drops of dry pyridine was allowed to stand at room temperature in a stoppered flask overnight. The reaction mixture was treated with water and extracted with ether. The ether extract was washed with 1 *N* aqueous HCl, saturated aqueous sodium bicarbonate solution, water, and brine and then dried. Solvent removal gave 0.176 g of crude ester as a brown oil. This material was chromatographed on 15 g of silica gel. Elution with 4:1 and 1:1 benzene–ether afforded 0.154 g (86.4%) of the ester mixture **20b** and **21b** as a brown oil (tlc, R_f 0.45): ir (film) 1750 (cyclopentanone C=O and ester C=O), 1670 (α,β-unsaturated ketone C=O), 1590, 1600 cm^{-1} (anisole); uv max (95% EtOH) 250 nm (ε 9180); pmr ($CDCl_3$) δ 7.30 (m, 6, aromatic), 6.89 (m, 3, aromatic), 6.01 (d of d, 1, *J* = 6, 8.5 Hz, HCO), 3.78 (s, 3, aromatic OCH_3), 3.46 (m, 3, aliphatic OCH_3), 1.11 ppm (s, 3, C_{7a} CH_3). The ^{19}F spectrum was obtained on a Varian XL-100 instrument at 94.1 MHz in $CDCl_3$ solution using CF_3CO_2H as an external standard. The spectrum showed essentially a single resonance band at 7.38 ppm downfield from TFA. The amount of 1*S* isomer present was <1%.

(1*R*)-2-[5,6,7,7a-Tetrahydro-(7a*S*)-methyl-1,5-dioxo-4-indanyl]-1-(3-methoxyphenyl)ethyl (*R*)-α-Methoxy-α-trifluoromethylphenylacetate and (1*S*)-2-[5,6,7,7a-Tetrahydro-(7a*R*)-methyl-1,5-dioxo-4-indanyl]-1-(3-methoxyphenyl)ethyl (*R*)-α-Methoxy-α-trifluoromethylphenylacetate (20a).—The racemic ketol **18a** was esterified with the acid chloride derived from (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid as described in the previous experiment. The product, after chromatographic purification, was a pale-yellow oil: tlc, R_f 0.43; ir (film) 1750 (cyclopentanone and ester C=O), 1670 (α,β-unsaturated ketone C=O), 1590, 1600 cm^{-1} (anisole); pmr ($CDCl_3$) δ 7.30 (m, 6, aromatic), 6.85 (m, 3, aromatic), 6.00 (m, 1, HCO), 3.78 (s, ~1.5, aromatic OCH_3 of 1*R* diastereomer), 3.74 (s, ~1.5, aromatic OCH_3 of 1*S* diastereomer), 3.47 (m, 3, aliphatic OCH_3), 1.12 ppm (s, 3, C_{7a} CH_3). The ^{19}F spectrum (same conditions as the previous experiment) showed two resonance bands of approximately equal intensity at δ 7.38 and 7.00 ppm downfield from external TFA. The δ 7.00 band was essentially absent in the spectrum of the mixture **20b** and **21b** (previous experiment).

(1*R*)-2-[5,6,7,7a-Tetrahydro-(7a*S*)-methyl-1,5-dioxo-4-indanyl]-1-(3-methoxyphenyl)ethyl 4-Bromobenzoate (22b).—A mixture of 2.6 g (8.3 mmol) of the optically active hydroxy enedione mixture **18b** and **19b**, 3.65 g (16.6 mmol) of 4-bromobenzoyl chloride, and 75 ml of dry pyridine was stirred at room temperature for 20 hr. The reaction mixture was then treated with 25 ml of water, allowed to stir for 15 min at room temperature before acidification with 3 *N* aqueous HCl, and then extracted with methylene chloride. The organic extracts were combined, washed once with water, twice with aqueous saturated sodium bicarbonate solution, and once with brine, then dried. Solvent removal gave a yellow solid residue which was chromatographed on 250 g of silica gel. The fractions eluted with 9:1 and 4:1 benzene–ether afforded 3.39 g (82.3%) of yellow solid (mixture of esters **22b** and **23b**).

This material was recrystallized four times from ethanol, giving 1.9 g (46.3%) of pure ester **22b** as colorless crystals: mp 126–127° (homogeneous on tlc analysis, R_f 0.47); $[\alpha]^{25}D$ −143.85° (*c* 0.5, C_6H_6); uv max (95% EtOH) 247 nm (ε 29,450); ir ($CHCl_3$) 1745 (cyclopentanone C=O), 1725 (ester C=O), 1670 (conjugated ketone C=O), 1590 cm^{-1} (anisole); mass spectrum *m/e* 496 (M^+); nmr ($CDCl_3$) δ 7.71 (A_2B_2 m, 4, *p*-BrC_6H_4C=O), 7.05 (m, 4, *m*-$CH_3OC_6H_4$), 6.08 (t, 1, *J* = 7 Hz, HCO), 3.78 (s, 3, OCH_3), 1.13 ppm (s, 3, C_{7a} CH_3). The spectra and tlc mobility were identical with those of the racemic ester **22a**.

Anal. Calcd for $C_{26}H_{25}BrO_5$: C, 62.78; H, 5.07; Br, 16.06. Found: C, 63.08; H, 5.01; Br, 15.97.

(1*R*,*S*)-2-[5,6,7,7a-Tetrahydro-(7a*S*,*R*)-methyl-1,5-dioxo-4-indanyl]-1-(3-methoxyphenyl)ethyl 4-Bromobenzoate (22a).—This material was prepared starting from the racemic ketol **18a** using the procedure described in the previous experiment. The pure ester was obtained in 82% yield as a pale-yellow solid, mp 139–140°. Crystals suitable for X-ray analysis were grown by slow crystallization from an ethanol–methylene chloride mixture. The ir, uv, nmr, and mass spectra as well as the tlc mobility were identical with those of the (+) form **22b**.

Anal. Calcd for $C_{26}H_{25}BrO_5$: C, 62.78; H, 5.07; Br, 16.06. Found: C, 63.04; H, 5.19; Br, 16.08.

(*S*)-(+)-7,7a-Dihydro-4-(*m*-methoxystyryl)-7a-methyl-1,5(6*H*)-indandione (24b).—A solution of 1.84 g (3.71 mmol) of the pure diketo ester **22b** and 0.3 g of *p*-toluenesulfonic acid monohydrate in 50 ml of toluene was stirred at reflux for 1.5 hr. The reaction mixture was cooled, diluted with ether, washed with aqueous saturated sodium bicarbonate solution and brine, and dried. Solvent removal gave an orange-yellow solid which was chromatographed on silica gel (60 g), yielding 0.9 g (81%) of an orange-yellow solid (eluted with 4:1 and 9:1 benzene–ether). Recrystallization from ethanol afforded 0.732 g (66.5%) of the diene **24b** as yellow needles, mp 111.5–112.5°. This material was homogeneous on tlc analysis, R_f 0.48. An analytical specimen was obtained as yellow needles, mp 112–112.5°, by further recrystallization of a sample from ethanol: $[\alpha]^{25}D$ + 164.35° (*c* 0.5, C_6H_6); uv max (95% EtOH) 219 nm (ϵ 23,520), 279(16,200), sh 315 (12,800); ir ($CHCl_3$) 1750 (cyclopentanone C=O), 1670 (α,β-unsaturated ketone), 1640 (C=C, w), 1600, 1585 cm^{-1} (anisole); nmr ($CDCl_3$) δ 6.95 (m, 6, aromatic and vinyl), 3.78 (s, 3, OCH_3), 1.34 ppm (s, 3, $C_{7a}CH_3$).

Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.07; H, 6.98.

(*R*,*S*)-7,7a-Dihydro-4-(*m*-methoxystyryl)-7a-methyl-1,5(6*H*)-indandione (24a).—This material was prepared starting from the racemic diketo ester **22a** using the procedure described in the preceding experiment. The analytical specimen was obtained by recrystallization from ether–ethanol as a yellow solid, mp 93–94°. The ir, uv, and nmr spectra as well as the tlc mobility were essentially identical with those of the (+) form **24b**.

Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.80; H, 6.69.

(*S*)-(+)-7,7a-Dihydro-4-[2-(3-methoxyphenyl)ethyl]-7a-methyl-1,5(6*H*)-indandione (25b). A. From Diene 24b.—The pure diene **24b** (0.407 g, 1.38 mmol) was hydrogenated in 25 ml of dry toluene in the presence of 0.2 g of 5% palladium on carbon.[38] After 25 min, 37.5 ml of hydrogen had been absorbed (34.4 ml theory) and the hydrogenation was stopped. The catalyst was filtered and washed with ether and the combined filtrate and washings were concentrated at reduced pressure. The residual, colorless oil was chromatographed on silica gel (20 g) to give 0.401 g (97.8%) of the enedione (eluted with 9:1 and 4:1 benzene–ether). A sample from a similar run was rechromatographed on silica gel and evaporatively distilled to give an analytical specimen of optically pure **25b** as a pale yellow oil, bp 170–185° (bath temperature) (0.05 mm), which was homogeneous on tlc analysis (R_f 0.45): $[\alpha]^{25}D$ + 195.05° (*c* 0.5, C_6H_6); uv max (95% EtOH) 220 nm (ϵ 11,470), 250 (9380), 278 (2630); ORD (*c* 0.5975, dioxane, 23°) $[\phi]_{700}$ +349.1°, $[\phi]_{589}$ +528.1°, $[\phi]_{371}$ +7099.6°, $[\phi]_{366}$ +6905.1°, $[\phi]_{357}$ +8655.7°, $[\phi]_{348}$ +6321.6°, $[\phi]_{341}$ +7391.4°, $[\phi]_{335}$ +6127.1°, $[\phi]_{325}$ +11969.8°, $[\phi]_{316}$ +4638.3°, $[\phi]_{313}$ +4787.9°, $[\phi]_{310}$ 0°, $[\phi]_{282}$ −43889.5°, $[\phi]_{260}$ −73415.2°, $[\phi]_{245}$ 0°, $[\phi]_{231}$ +74200.8°, and $[\phi]_{210}$ (last) 0°; ir ($CHCl_3$) 1750 (cyclopentanone C=O), 1665 (α,β-unsaturated ketone C=O), 1600, 1585 cm^{-1} (anisole); nmr ($CDCl_3$) δ 7.16 (m, 1, aromatic), 6.68 (m, 3, aromatic), 3.75 (s, 3, OCH_3), 1.18 ppm (s, 3, $C_{7a}CH_3$).

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.21; H, 7.47.

B. From Enone 26b.—A 2-g (8 mmol) sample of the enone **26b**[20] (94.5% optically pure) was alkylated with *m*-methoxyphenethyl tosylate[24] (2.42 g, 7.96 mmol) using the procedure of Whitehurst, *et al.*[24] The crude alkylate was hydrolyzed[24] and the resulting red, oily product (2.3 g) was chromatographed on 125 g of silica gel. Elution with 1:1 benzene–ether gave 0.758 g (31.6%) of oily (1*S*,7a*S*)-1-hydroxy-7,7a-dihydro-4-[2-(3-methoxyphenyl)ethyl]-7a-methyl-5(6*H*)-indanone: tlc R_f 0.24; ir (film) 3425 (OH), 1650 (α,β-unsaturated ketone C=O), 1600, 1585 cm^{-1} (anisole).

A solution of this material in 25 ml of acetone was stirred with ice-bath cooling while 0.8 ml of Jones reagent[25] was added dropwise from a syringe over a 5-min period. The resulting mixture was stirred at 0–5° for 5 min, then decomposed with aqueous sodium bisulfite solution and worked up with ether, giving 0.754 g of brown oil. This material was chromatographed on 37.5 g of silica gel. The fractions eluted with 19:1 benzene–ether afforded 0.6 g of yellow, oily enedione which was homogeneous on tlc analysis, R_f 0.44. Evaporative distillation gave 0.532 g (70.5%) of viscous, pale-yellow, oily **25b**: bp 195–200° (bath temperature) (0.1 mm); $[\alpha]^{25}D$ +185° (*c* 0.5, C_6H_6); uv max (95% EtOH) 220 nm (ϵ 11,160), 250 (9580), 278 (2460); mass spectrum *m/e* 298 (M^+); ORD (*c* 0.4200, dioxane, 23°) $[\phi]_{700}$ +312.2°, $[\phi]_{589}$ +489.6°, $[\phi]_{370}$ +6754.7°, $[\phi]_{365}$ +6655.3°, $[\phi]_{356}$ +8244.7°, $[\phi]_{348}$ +5860.7°, $[\phi]_{340}$ +6953.3°, $[\phi]_{334}$ +5662.0°, $[\phi]_{325}$ +11068.6°, $[\phi]_{316}$ +4044.3°, $[\phi]_{313}$ +4257.1°, $[\phi]_{310}$ 0°, $[\phi]_{280}$ −37803.4°, $[\phi]_{260}$ −57471.4°, $[\phi]_{246}$ 0°, $[\phi]_{231}$ +66411.4°, and $[\phi]_{210}$ (last) 0°. The ir and nmr spectra were essentially identical with those of the material produced in part A above. The $[\alpha]D$ when corrected for the optical purity of the starting material corresponds to a value of +195.9° for optically pure material (lit.[7d] $[\alpha]^{25}D$ +181°).

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.41; H, 7.32.

C. From the Mixture of Ketols 18b and 19b.—A solution of 0.493 g (1.57 mmol) of the hydroxy enedione mixture **18b** and **19b** and 50 mg of *p*-toluenesulfonic acid monohydrate in 15 ml of toluene was stirred and heated at reflux for 20 min. The reaction mixture was cooled, diluted with ether, washed with saturated aqueous sodium bicarbonate solution and brine, then dried and filtered. Solvent removal gave the crude diene (mixture of **24a** and **24b**) as a red oil which was hydrogenated in 30 ml of toluene in the presence of 0.15 g of 5% palladium on carbon.[38] After 15 min, 39.2 ml of hydrogen had been absorbed (39.3 ml theory) and the hydrogenation was stopped. The catalyst was filtered and washed with ether and the combined filtrate and washings were concentrated at reduced pressure to give 0.46 g of the crude enedione as a red oil. This material was chromatographed on silica gel (50 g) to give 0.352 g of an orange oil (eluted with 9:1 benzene–ether). Evaporative distillation gave 0.335 g (71.6%) of a yellow oil: bp 145–175° (bath temperature) (0.01 mm); $[\alpha]^{25}D$ +149.68° (*c* 0.5, C_6H_6); uv max (95% EtOH) 249 nm (ϵ 8940). Preparative gas chromatographic purification of a sample prepared in this way was carried out using an F & M Model 320 instrument on an 8 ft × 0.5 in. o.d. stainless steel column packed with 10% SE-30 silicone on 70–80 mesh Chromosorb W AW-DMCS at 280° with a helium carrier gas flow rate of 2–2.5 ml/sec. The major peak (94%, retention time 8.8 min) was collected and evaporative distillation of this material gave a mixture of the *S* isomer (**25b**) and racemic enedione (**25a**) as a pale yellow oil: bp 150–180° (bath temperature) (0.03 mm); $[\alpha]^{25}D$ +153.60° (*c* 0.5, C_6H_6); uv max (95% EtOH) 219 nm (ϵ 11,115), 250 (8770), 279 (2470); ORD (*c* 0.3178, dioxane, 23°) $[\phi]_{700}$ +254.8°, $[\phi]_{589}$ +396.4°, $[\phi]_{370}$ +5346.3°, $[\phi]_{366}$ +5281.1°, $[\phi]_{355}$ +6519.8°, $[\phi]_{349}$ +4824.7°, $[\phi]_{342}$ +5607.4°, $[\phi]_{335}$ +4694.3°, $[\phi]_{324}$ +8662.1°, $[\phi]_{313}$ +2980.5°, $[\phi]_{309}$ 0°, $[\phi]_{271}$ −30736.3°, $[\phi]_{258}$ −43030.8°, $[\phi]_{244}$ 0°, $[\phi]_{230}$ +45173°, and $[\phi]_{208}$ (last) +2528.5°. The ir and nmr spectra as well as the tlc mobility of this material were identical with those of the products from part A and B and with those of the racemic modification **25a**[18] described in the following experiment. The observed rotation corresponds to an optical purity of 78.5%.

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.21; H, 7.56.

(*R*,*S*)-7,7a-Dihydro-4-[2-(3-methoxyphenyl)ethyl]-7a-methyl-1,5(6*H*)-indandione (25a).—A 1-g (3.184 mmol) sample of ketol **18a** was dehydrated and the resulting diene was hydrogenated as described in part C of the preceding experiment. After purification by chromatography and evaporative distillation there was obtained 0.675 g (71.3%) of racemic enedione **25a** as a yellow oil, bp 180–220° (bath temperature) (0.1 mm), which was homogeneous on tlc analysis: ir (film) 1740 (cyclopentanone C=O), 1660 (α,β-unsaturated ketone C=O), 1600 (anisole), 780, 690 cm^{-1}; uv max (95% EtOH) 220 nm (ϵ 10,400), 250 (8300) [lit.[18] bp 160–190° (bath temperature) (0.05 mm); uv max 249 nm (ϵ 9000); ir 1740, 1660, 1600, 780, and 690 cm^{-1}]. The

(38) A 5% palladium-on-carbon catalyst prepared at F. Hoffmann-La Roche and Co., AG, Basle, Switzerland, and designated AK-4 was employed for this hydrogenation.

physical spectra and tlc mobility of this material were essentially identical with those of the optically active form described in the preceding experiment.

(+)-**3-Methoxyestra-1,3,5(10),9(11)-tetraen-17-one (27b).**—The sequence of Smith, *et al.*,[18] was employed. A solution of 0.87 g (2.92 mmol) of the optically pure enedione **25b** (prepared from diene **24b**) in 15 ml of ethanol was stirred and cooled in an ice–salt bath to −8° while a solution of 30 mg (0.793 mmol) of sodium borohydride in 25 ml of ethanol was added dropwise over a 15-min period keeping the temperature below 0°.[29] The reaction mixture was then stirred for 15 min at *ca.* −3°. The pH was adjusted to 6–7 with 3 *N* aqueous HCl and after diluting with brine, the reaction mixture was worked up with ether, giving a colorless oil. This material was chromatographed on silica gel (100 g), affording 770.3 mg (88.0%) of (1*S*,7a*S*)-1-hydroxy-7,-7a-dihydro-4-[2-(3-methoxyphenyl)ethyl]-7a-methyl-5(6*H*)-indanone as a pale yellow oil (eluted with 1:1 and 1:3 benzene–ether). The ir spectrum and tlc mobility of this material were identical with those of the sample prepared from enone **26b** as described above.

This hydroxy ketone was hydrogenated in 30 ml of absolute ethanol in the presence of 0.2 g of 5% palladium on carbon.[38] After 2.25 hr, 66 ml of hydrogen had been absorbed (64 ml theory) and the hydrogenation appeared to have stopped. The catalyst was filtered and washed well with ethanol and the combined filtrate and washings were concentrated at reduced pressure to give a colorless oil. Chromatography on 75 g of silica gel afforded 464 mg (60.1%) of the major component as a colorless oil (eluted with 1:2 and 1:4 benzene–ether): ir (film) 3430 (OH), 1710 (cyclohexanone C=O), 1600, 1585 cm^{-1} (anisole); tlc R_f 0.29.

A solution of this material in 15 ml of acetone was stirred with ice-bath cooling at 0° while 1.25 ml of Jones reagent[26] was added dropwise from a syringe. The reaction mixture was stirred for 5 min at 0–5°, then the excess oxidant was decomposed with 2-propanol. The reaction mixture was worked up with ether, giving a pale-yellow oil. Chromatography on silica gel (50 g) afforded 434 mg (93.8%) of diketone as a pale-yellow oil (eluted with 4:1 and 1:1 benzene–ether) (tlc R_f 0.46): ir (film) 1740 (cyclopentanone C=O), 1715 (cyclohexanone C=O), 1600, 1585 cm^{-1} (anisole).

A solution of this diketone in 10 ml of methanol was stirred at room temperature while 2 ml of 10 *N* aqueous HCl was added. The reaction mixture became warm and after 10 min, a white precipitate was present. After 4 hr of stirring at room temperature, the reaction mixture was chilled at 0° for 1.5 hr. The white precipitate was filtered, washed with cold methanol, and dried under vacuum to give 247.9 mg of white solid, mp 130–133°. Recrystallization from methanol gave 156.8 mg (38.5%) of the pure ketone **27b** as colorless needles: mp 142.5–144°; homogeneous on tlc analysis, R_f 0.50; $[\alpha]^{25}D$ +290.92° (*c* 0.5, $CHCl_3$); ir ($CHCl_3$) 1735 (cyclopentanone C=O), 1605 cm^{-1} (anisole); uv max (95% EtOH) 263 nm (ε 19,300), 297 (3400), infl 310 (2220); nmr ($CDCl_3$) δ 7.52 (d, 1, aromatic), 6.68 (m, 2, aromatic), 6.13 (m, 1, C_{11} H), 3.76 (s, 3, OCH_3), 0.92 ppm (s, 3, C_{13} CH_3); ORD (*c* 0.3034, dioxane, 23°) $[\phi]_{700}$ +650.6°, $[\phi]_{589}$ +948.1°, $[\phi]_{321}$ +18812.4°, $[\phi]_{250}$ 0°, $[\phi]_{243}$ −1858.9°, $[\phi]_{240}$ 0°, $[\phi]_{226}$ +11153.6°, $[\phi]_{220/224}$ +8365.2°, $[\phi]_{216}$ 0°, and $[\phi]_{210}$ (last) −9294.7° [lit.[26] mp 142–144°; $[\alpha]^{25}D$ +289° ($CHCl_3$); uv max (EtOH) 263 nm (ε 17,300)].

Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.53; H, 7.78.

(1*R*,*S*)-2-[(1*S*,*R*)-**Hydroxy-5,6,7,7a-tetrahydro-(7a*S*,*R*)-methyl-5-oxo-4-indanyl]-1-(3-methoxyphenyl)ethanol (28a).**—The procedure of Oliveto, *et al.*[29] was employed. A mixture of 2.76 g (8.8 mmol) of ketol **18a** and 28 ml of ethanol was stirred at −10° while 9.2 ml (2.67 mmol) of 0.29 *M* ethanolic sodium borohydride was added dropwise over a 10-min period. After stirring at −5 to 5° for 50 min, the reaction mixture was decomposed with 3 *N* aqueous HCl and worked up with ether, giving 2.91 g of diol **28a** as a tan foam (tlc 0.15): ir (film) 3450 (OH), 1640 cm^{-1} (α,β-unsaturated ketone C=O).

Hydrogenation of this material over 5% palladium on carbon[38] in ethanol was not selective. When it was allowed to proceed to completion, about 2 molar equiv of hydrogen was absorbed. The crude product was reoxidized[25] and the resulting ketone mixture was chromatographed on silica gel. The early fractions eluted with 19:1 benzene–ether gave a yellow oil which appeared to be a mixture of compounds lacking both the benzylic hydroxyl and cyclohexanone functions: ir (film) 1740 (cyclopentanone C=O), 1600 cm^{-1} (anisole); uv max (95% EtOH) 215 nm (ε 6375), 271 (1360), 278 (1360); mass spectrum *m/e* 284 (M^+), 286 (M^+). The later fractions eluted with 19:1 benzene–ether and 9:1 benzene–ether afforded a pale-yellow oil which was a mixture of isomers of (±)-3a,4,7,7a-tetrahydro-4-[2-(3-methoxyphenyl)ethyl]-7a-methyl-1,5(6*H*)-indandione: ir (film) 1750 (cyclopentanone C=O), 1710 (cyclohexanone C=O), 1600 cm^{-1} (anisole); uv max (95% EtOH) 215 nm (ε 7400), 271 (1760), 278 (1680); mass spectrum *m/e* 300 (M^+). The ratio of these products varied considerably from run to run.

(1*R*,*S*)-2-[5,6,7,7a-**Tetrahydro-(7a*S*,*R*)-methyl-1,5-dioxo-4-indanyl]-1-(3-methoxyphenyl)ethyl Acetate (29a).**—A 0.5-g (1.59 mmol) sample of ketol **18a** was allowed to stand at room temperature in a solution of 5 ml of pyridine and 2.5 ml of acetic anhydride for 27 hr. The solvents were partially removed at reduced pressure and the residue was poured into saturated aqueous sodium bicarbonate and worked up with ether (the ether extracts were additionally washed twice with 1 *N* HCl), giving 0.573 g (100 + %) of the oily acetate **29a**. This material showed a single spot on tlc analysis, R_f 0.4. After drying thoroughly, it still contained some ether and showed the following spectral properties: uv max (95% EtOH) 220 nm (ε 11,010), 249 (9190), 275 (3040), 281 (2620); ir ($CHCl_3$) 1750 (cyclopentanone, ester C=O), 1670 (α,β-unsaturated ketone C=O), 1600 cm^{-1} (anisole); mass spectrum *m/e* 356 (M^+); nmr ($CDCl_3$) δ 5.80 (t, 1, *J* = 7 Hz, HCO), 3.78 (s, 3, OCH_3), 2.02 (s, 3, CH_3C=O), 1.15 ppm (s, 3, C_{7a} CH_3). This material was used without further purification.

(1*R*,*S*)-2-[(1*S*,*R*)-**Hydroxy-5,6,7,7a-tetrahydro-(7a*S*,*R*)-methyl-5-oxo-4-indanyl]-1-(3-methoxyphenyl)ethyl Acetate (30a).**—The procedure of Oliveto, *et al.*,[29] was employed. A 0.526-g (1.48 mmol) sample of the crude acetate **29a** from the preceding experiment was dissolved in 4.6 ml of ethanol and the solution was stirred at −10° while 1.56 ml of a 0.291 *M* ethanolic sodium borohydride solution was added dropwise from a syringe. The resulting mixture was stirred in the cold for 40 min and then decomposed with 1 *N* aqueous HCl. Work-up with ether gave 0.545 g of a yellow gum which was homogeneous on tlc analysis (R_f 0.26): ir (film) 3400 (OH), 1730 (ester C=O), 1650 (α,β-unsaturated ketone C=O), 1600 (anisole), 1230 cm^{-1} (acetate); uv max (95% EtOH) 219 nm (ε 9210), 248 (9300); nmr ($CDCl_3$) δ 7.10 (m, 4, aromatic), 5.84 (t, 1, *J* = 8 Hz, HCO), 3.82 (s, 3, OCH_3), 2.04 (s, CH_3C=O), 1.02 ppm (s, 3, C_{7a} CH_3); mass spectrum *m/e* 358 (M^+). This material was used without further purification.

(±)-**3-Methoxyestra-1,3,5(10),6,8-pentaen-17-one [(±)-Equilenin 3-Methyl Ether] (33a).**—A 0.742-g (2.08 mmol)sa mple of hydroxy keto ester **30a** was hydrogenated in 30 ml of ethanol over 0.2 g of 5% palladium on barium sulfate at 1 atm and room temperature. After 5.67 hr, 53 ml of hydrogen had been consumed (theory for 1 molar equiv, 52 ml). The catalyst was filtered and washed with fresh ethanol. The combined filtrate and washes were concentrated at reduced pressure, giving 0.736 g of a cloudy glass, uv max (95% EtOH) 244 nm (ε 4760). Tlc analysis showed six spots. This material was chromatographed on 37.5 g of silica gel. Elution with 9:1 benzene–ether–4:1 benzene–ether gave various materials derived from hydrogenolysis of the benzylic acetate and enone functions as evidenced by lack of ester or cyclohexanone absorptions in the ir spectra. Elution with 1:1 benzene–ether gave 109 mg of an oil which was a mixture of isomers of ketol ester **31a** (tlc, R_f 0.29): ir (film) 3450 (OH), 1730 (ester C=O), 1700 (cyclohexanone C=O), 1590 cm^{-1} (anisole) (no conjugated ketone present). The later fractions eluted with 1:1 benzene–ether and ether gave 0.163 g of starting acetate **30a** (tlc, R_f 0.25). The mixture fractions (0.204 g) which contained the desired material were rechromatographed on 10 g of silica gel affording an additional 0.082 g of **31a** and 0.052 g of starting material. In this way, a total of 0.191 g (25.5%; 36% based on recovered starting material) of **31a** and 0.215 g (29%) of recovered **30a** was obtained.

When this hydrogenation was carried out with palladium on carbon, palladium on calcium carbonate, or platinum or rhodium on alumina, only trace amounts of **31a** were produced.

The above ketol ester **31a** (0.191 g, 0.53 mmol) was dissolved in 5 ml of acetone. The resulting solution was stirred and cooled to 0–5° while 0.19 ml of Jones reagent[25] was added from a syringe. The resulting red mixture was stirred for several minutes, then decomposed with 2-propanol. Work-up with ether gave 0.171 g of the oily diketo ester mixture **32a** which was homogeneous on tlc analysis (R_f 0.5): ir (film) 1735 (ester and

cyclopentanone C=O), 1700 (cyclohexanone C=O), 1590 cm^{-1} (anisole). Material from a similar run showed the following spectral properties: uv max (95% EtOH) 215 nm (ϵ 6960), 272 (2030), 279 (1840); nmr ($CDCl_3$) δ 6.85 (m, 4, aromatic), 5.90 (t, 1, J = 8 Hz, HCO), 3.87 (s, 3, OCH_3), 2.02 (s, CH_3C=O), 1.26 (s, C_{7a} CH_3, minor isomer), 1.02 ppm (s, C_{7a} CH_3, major isomer); mass spectrum m/e 358 (M^+).

An ice-cold solution of this diketo ester (0.171 g, 0.475 mmol) in 3 ml of methanol was stirred while 0.625 ml of 10 *N* aqueous HCl was added. The resulting solution was stirred at 0–5° for 10 min and then at room temperature for 3.5 hr. Work-up with ether gave 0.162 g of oily product. This material was stirred and heated at reflux in 5 ml of benzene containing 25 mg of *p*-toluenesulfonic acid monohydrate. After cooling the solution was diluted with ether, washed once with aqueous sodium bicarbonate solution, dried, and concentrated at reduced pressure, giving 138 mg of semicrystalline residue. Chromatography on 7.5 g of silica gel gave 63 mg (42.5% based on **31a**) of pure, racemic equilenin 3-methyl ether (**33a**) (eluted with 49:1 benzene–ether; tlc, one spot, R_f 0.57). Recrystallization from ethanol gave colorless plates, mp 183–186° (lit.[30] mp 186°; lit.[31,33] mp 185–186°; lit.[32] mp 188–190°). The ir, uv, and nmr spectra and tlc mobility of this racemic material were identical with those of *d*-equilenin methyl ether, mp 195–196°, prepared by methylation of (+)-equilenin (Searle) as described by Wilds, *et al.*[33]

Crystallography.—Crystals of **22a** were obtained from an ethanol–methylene chloride mixture as well-formed prisms. The crystal data are a = 14.67 (1), b = 7.09 (1), c = 24.81 (3) Å, β = 116.90 (5)°, d_{obsd} (aqueous KI) = 1.42, d_{calcd} = 1.435 g cm^{-3} for Z = 4, space group $P2_1/c$.

The intensities of 4571 independent X-ray diffraction maxima with $2\theta < 140°$ were measured on a Hilger-Watts Model Y290 four-circle diffractometer using Ni-filtered Cu Kα radiation. A rapid, stationary crystal–stationary detector technique was used to collect the data and an empirical correction was applied to convert the peak top data to integrated scan data. A total of 3531 reflections were significantly greater than background and these data were used for the structure analysis. The dimensions of the data crystal were 0.35 × 0.35 × 0.45 mm. The data were corrected for absorption (μ = 29.8 cm^{-1}).

The structure was solved by the heavy atom method. Refinement of the structure was carried out by full matrix least squares. All atoms had isotropic temperature factors except the bromine, which was assigned anisotropic thermal parameters; hydrogen atoms were not included. At the conclusion of the refinement, R = 0.132. A difference Fourier calculated at this point had no features greater than 1.0 electron/Å^3 in magnitude.[39]

Acknowledgments.—We wish to express our gratitude to the personnel of the Physical Chemistry Department of Hoffmann-La Roche Inc., Nutley, N. J., for carrying out many of the spectral and microanalytical determinations required in this work and to the members of the Kilo Laboratory who assisted in the preparation of certain of the starting materials.

Registry No.—**5a**, 40901-47-1; **5b**, 38102-79-3; **5c**, 38102-77-1; **10**, 38102-72-6; **11**, 38102-67-9; **12a**, 38171-50-5; **13a**, 38171-49-2; **13b**, 40901-54-0; **13b** (*R*)-(+)-α-methylbenzylamine salt, 38102-75-9; **13c**, 40903-49-9; **13c** (*S*)-(−)-α-methylbenzylamine salt, 38171-48-1; **14a**, 38102-69-1; **14b**, 40901-59-5; **15**, 38102-70-4; **16**, 38102-71-5; **18a**, 40901-62-0; **18b**, 38680-53-4; **19b**, 38680-54-5; **20a**, 40903-58-0; **20b**, 40901-66-4; **21b**, 40903-60-4; **22a**, 40901-68-6; **22b**, 38680-56-7; **24a**, 38680-42-1; **24b**, 38680-57-8; **25a**, 18300-15-7; **25b**, 15375-09-4; **26b**, 17780-12-0; **27b**, 1670-49-1; **28a**, 40901-76-6; **29a**, 40903-70-6; **30a**, 40901-78-8; **31a**, 38680-49-8; **32a**, 38680-50-1; **33a**, 4820-56-8; (*R*)-(+)-α-methylbenzylamine, 3886-69-9; 2-methyl-1,3-cyclopentanedione, 765-69-5; (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid, 20445-31-2; *p*-toluenesulfonic acid, 104-15-4.

Supplementary Material Available.—Listings of structure factors and atomic parameters will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-3229.

(39) See paragraph at end of paper regarding supplementary material.

The Stereocontrolled Synthesis of *trans*-Hydrindan Steroidal Intermediates

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Received February 15, 1973

Catalytic hydrogenation of simple $\Delta^{3a(4)}$-indan derivatives (*e.g.*, **1a**) gave mainly (88.5%) the thermodynamically favored cis-fused bicyclic products. In the presence of a β-oriented bulky C-1 substituent ~30% of trans-fused derivatives and with an additional bulky substituent at C-4 ~50% of trans-fused hydrogenation products could be obtained. With a carboxylic acid or a carboxylic ester substituent at C-4 practically full stereocontrol has been achieved to yield the desired trans-fused bicyclic compounds (**8** and **13**). A theoretical explanation of the stereochemical results has been included.

During the course of an investigation of a new total synthesis of steroidal compounds the problem of the stereocontrolled preparation of *trans*-hydrindan derivatives became of prime importance. These bicyclic compounds correspond to the CD portion of the steroidal skeleton, and if properly functionalized they may become suitable building blocks of a new totally synthetic scheme to obtain steroidal compounds.

It has been previously reported[2a] that indan derivatives, *e.g.*, the bicyclic unsaturated keto alcohol **1a**, gave, under a variety of hydrogenation conditions, only the thermodynamically more stable C/D cis keto alcohol **2**. We found 88.5% of cis compound **2** in the reaction mixture by vpc, which is in fair agreement with a more recent publication reporting ~80% of **2** as estimated by nmr spectroscopy.[2b]

It was of interest to discover whether the desired C/D trans stereoisomer could be obtained by the catalytic hydrogenation of a properly modified and substituted bicyclic system. The *tert*-butyl ether **1b** has therefore been subjected to catalytic hydrogenation under a variety of reaction conditions. It was hoped that preferential α-side attack would occur owing to the β-oriented bulky substituent at the C-1 position of the molecule. The *tert*-butyl ether group was removed by hydrolysis of the reduction products, and the resulting mixture of **2** and **3** was subjected to fractionation by

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(2) (a) C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, 4547 (1960); (b) K. H. Baggaley, S. G. Brooks, J. Green, and B. T. Redman, *J. Chem. Soc. C*, 2671 (1971).

preparative vpc. The desired C/D trans bicyclic hydroxy ketone **3** was thus obtained in 96% purity.

The best result in the catalytic hydrogenation was obtained by using a 5% Pd-on-carbon catalyst and cyclohexane as solvent. This yielded approximately 30% of the desired C/D trans bicyclic hydroxy ketone **3** as shown by vpc and by nmr analysis (Table I).

TABLE I

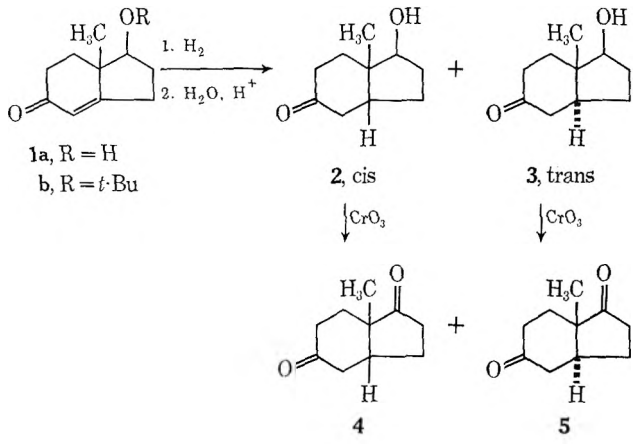
CATALYTIC HYDROGENATION OF **1b** FOLLOWED BY REMOVAL OF *tert*-BUTYL GROUP

		Vpc		Nmr	
Catalyst	Solvent	cis, %	trans, %	cis, %	trans, %
Pd/C	Cyclohexane	60.5	34.5	70	30
Pd/C	*n*-Hexane	62.5	27.5	80	20
$Pd/BaSO_4$	Cyclohexane	72.0	24.0		

Oxidation of the hitherto unknown trans-fused keto alcohol **3** gave the trans bicyclic diketone **5**, a crystalline solid after purification by preparative thin layer chromatography. This compound was identical with a sample prepared by an independent route.[2b]

Authentic samples of the C/D cis compounds **2** and **4** were also prepared for reference by literature procedures[2a] (Scheme I).

SCHEME I[a]



[a] All compounds reported in this paper are racemic. For convenience, only one enantiomer is shown.

Data of nmr spectroscopy and of vpc are compiled in Table II. In this series of compounds the additivity

TABLE II

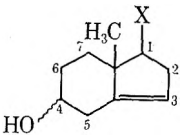
NMR AND VPC DATA OF BICYCLIC COMPOUNDS

Compd	δ (7a-methyl)	$\Delta W_{h/2}$	Retention time, min
2, cis keto alcohol	1.17	0.8	17.5
4, cis diketone	1.24	0.5	10.3
3, trans keto alcohol	1.02	1.2	18.3
5, trans diketone	1.12	1.55	11.7

of the chemical shifts of the methyl signals did not convincingly support the cis or trans configuration of the system. The nmr peak width at half-height ($W_{h/2}$) of the angular methyl group was therefore measured and compared with the $W_{h/2}$ of the tetramethylsilane signal ($\Delta W_{h/2}$).[3] In agreement with results of decalin derivatives,[4] it was found that the $\Delta W_{h/2}$ values were greater for the trans compound than for the corresponding cis isomers.

The vpc results were also in agreement with the stereochemical assignments. As expected, the C/D trans-fused compounds **3** and **5** showed longer retention times in comparison to the corresponding C/D cis-fused derivatives **2** and **4**, respectively. This is due to the increased adsorption of the relatively more planar trans-fused derivatives.[5]

Next we turned our attention to the catalytic hydrogenation of an isolated 3(3a) double bond in the bicyclic system. It has been reported[6] that the 1-carbomethoxy derivative **6a** gave 32% of the desired C/D trans-fused derivative upon catalytic reduction. Starting with the bicyclic compound **1a** we prepared the related 1-acetoxy and 1-hydroxy derivatives (**6b** and **6c**) using literature procedures,[6] and subjected them to



6a, X = CO_2CH_3
b, X = $OCOCH_3$
c, X = OH

catalytic hydrogenation. We obtained in each case only a C/D cis-fused derivative, as shown by conversion to the cis diketone **4**. A similar result has recently been reported[7] in the catalytic hydrogenation of the bicyclic Δ3(3a)-diol (**6c**).

All of these results pointed to the difficulties in trying to improve the yield of the desired C/D trans system in a catalytic hydrogenation reaction. It was also anticipated that subsequent alkylation would occur mainly at the undesired C-6 position, because of the preference of trans-fused bicyclic derivatives to enolize in that direction.[8]

On the other hand, the introduction of an appropriate group (*e.g.*, carboxylic ester function) at the C-4 position should activate that site toward alkylation reactions. It may also assist the stereocontrol of the catalytic hydrogenation, since we have previously shown that with a bulky substituent at the C-4 position a reasonable amount (at least 50%) of the desired C/D trans bicyclic derivative could be obtained.[9]

The unsaturated β-keto acid **7** was therefore prepared by carbonation of the conjugate anion derived from the bicyclic *tert*-butyl ether **1b** (Scheme II). The possibility of an isomeric C-6 substituted β-keto acid *via* carbonation of the homoannular conjugate anion was excluded by nmr spectroscopy; there was no vinylic proton in the spectrum of **7**.

Catalytic hydrogenation of **7** gave the saturated β-keto acid **8** in excellent yield. The α-equatorial configuration of the carboxyl group was established by nmr

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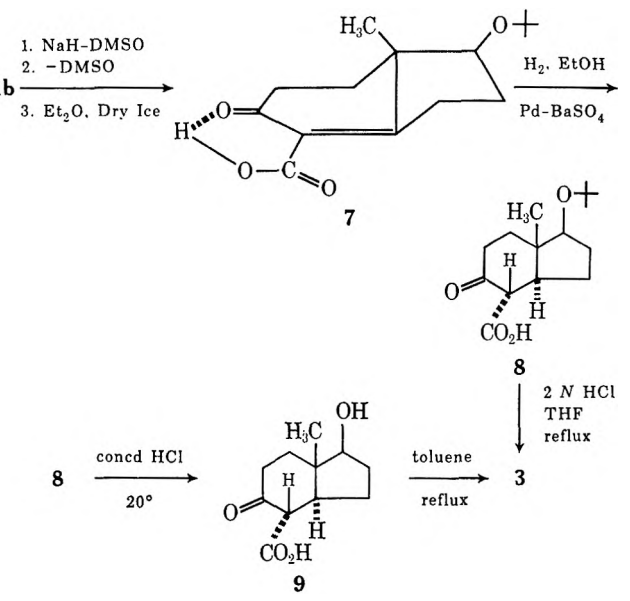
SCHEME II



spectroscopy; the C-4 proton appeared as a doublet centered at δ 3.38. The large coupling constant ($J_{3aH,4H}$ = 13 Hz) confirmed the trans diaxial relationship of the C-3a and C-4 protons. The C/D trans stereochemistry of the β-keto acid **8** was proven by conversion to the C/D trans bicyclic hydroxy ketone **3** *via* hydrolysis and decarboxylation.

The same compound (**3**) could also be obtained upon hydrolysis of the *tert*-butyl ether group of **8** followed by thermal decarboxylation of the hydroxy β-keto acid **9** in refluxing toluene. The remarkable stability of the β-keto acid **8** toward concentrated hydrochloric acid is most likely due to the C/D trans ring fusion, which would not favor the introduction of a 4(5) double bond[8] and thus the formation of the cyclic transition state assumed for the decarboxylation of β-keto acids.[10]

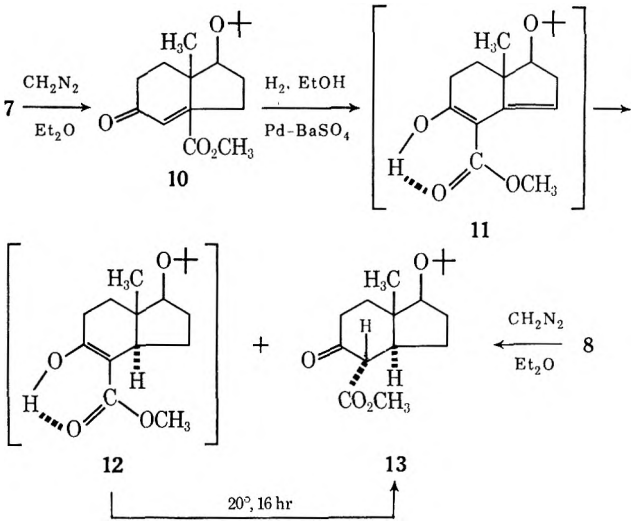
It was thus shown that the unsaturated β-keto acid **7** could be hydrogenated without substantial decarboxylation to the desired C/D trans-fused β-keto acid **8** of high purity. This major improvement over our previous results is undoubtedly due to a favorable combination of several factors. The infrared spectrum of the unsaturated β-keto acid **7** [ν_{max} 1733 (carboxyl carbonyl), 1620 (α,β-unsaturated carbonyl), 1600 cm^{-1} (olefinic double bond) in chloroform] showed hydrogen bonding between the conjugated carbonyl and the sp^2-oriented carboxylic acid group, thereby forming a pseudo B ring *via* chelation. The addition of piperidine relieved hydrogen bonding, and the α,β-unsaturated carbonyl group appeared at its normal position, *i.e.*, ν_{max} 1660 cm^{-1}.

If it were possible for the molecule to exist either in the half-chair or in the 1,2-diplanar conformation,[11] the hydrogen-bonded structure would most certainly prefer the half-chair conformation to relieve steric interactions between the pseudo B ring and the five-membered ring. Hydrogenation of the unsaturated β-keto acid in this rather planar conformation **7** should then favor addition of hydrogen from the less hindered bottom side of the molecule, opposite the β substituents at the C-1 and C-7a positions, to give a C/D trans-fused system.

According to a theory developed for the catalytic hydrogenation of α,β-unsaturated bicyclic ketones, 1,4 addition of hydrogen should lead to preferential cis hydrogenation, while 1,2 addition should give increased quantities of the trans-fused product.[12] In hydroxylic solvents hydrogen bonding to the keto group should inhibit 1,4 addition according to this theory. Intramolecular hydrogen bonding in the unsaturated β-keto acid **7** should thus correspond to the latter condition and give increased quantities of the trans-fused product owing to the strong inhibition of 1,4 addition, as was indeed the case.

The unsaturated β-keto ester **10** was then prepared by treating **7** with the theoretical amount of diazomethane in ether (Scheme III). The compound **10** was fully

SCHEME III



ketonic as indicated by ir, uv, and nmr spectroscopy. Catalytic hydrogenation of **10** with the theoretical amount of hydrogen yielded a reduction product which gave a strong ferric chloride test. The ultraviolet absorption [λ_{max}^{EtOH} 258 nm (ϵ 8050)] and the infrared spectrum with two relatively small bands at ν_{max} 1640 and 1601 cm^{-1} indicated the presence of an enolic component (**12**) in the mixture. However, after 16 hr at 20°, this mixture no longer showed an ultraviolet absorption, nor did it give a ferric chloride test. Its infrared and nmr spectra were superimposable with those of an authentic sample of **13** prepared from the C/D trans β-keto acid **8** with diazomethane in ether. The ease of the tautomerization of **12** → **13** is in agreement with the trans fusion of the ring system. That the β-keto ester **13** was fully ketonic, showed no uv absorption, and gave no ferric chloride test was to be expected in analogy with literature examples.[13a-c]

The rate of the catalytic hydrogenation of the unsaturated β-keto ester **10** was approximately four times

(10) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1965, p 347.

(11) Such conformers have been suggested for the A/B ring system of 3-keto-Δ^4 steroids; *cf.* E. Toromanoff in "Topics in Stereochemistry," Vol. 2, N. L. Allinger and E. L. Eliel, Ed., Interscience, New York, N. Y., 1967, p 168.

(12) R. L. Augustine, D. C. Migliorini, R. E. Foscante, C. S. Sodano, and M. J. Sisbarro, *J. Org. Chem.*, **34**, 1075 (1969).

(13) (a) E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.*, **81**, 5601 (1959); (b) T. A. Spencer, T. D. Weaver, and W. J. Greco, Jr., *J. Org. Chem.*, **30**, 3333 (1965); (c) T. A. Spencer, R. M. Villarica, D. L. Storm, T. D. Weaver, R. J. Friary, J. Posler, and P. R. Shafer, *J. Amer. Chem. Soc.*, **89**, 5497 (1967).

slower than that of the unsaturated β-keto acid **7** under otherwise identical reaction conditions. With three times as much catalyst the reaction rates of the catalytic hydrogenation of **10** and of **7** became identical. The difference in the rates and also the appearance of an enolic reaction product in the hydrogenation of the β-keto ester **10** suggests the reduction of the 3(3a) double bond of intermediate **11** in the case of the β-keto ester **10**. With the β-keto acid **7**, however, hydrogenation proceeds *via* saturation of the 3a(4) double bond (*cf.* Schemes II and III, respectively). Pseudo B ring formation has to involve a proton at C-3 in the case of the β-keto ester **10**, while no such mobilization is necessary with the β-keto acid **7**, where the molecule already exists with a chelated pseudo B ring structure owing to the proton available at the carboxylic acid function.

It should be mentioned that it was shown earlier[14] that a C/D trans bicyclic intermediate can be obtained *via* hydrogenation of the copper chelate of a bicyclic β-keto ester, (±)-5,6,7,7a-tetrahydro-7aβ-methyl-1,5-dioxo-4-indanecarboxylic acid ethyl ester.[15] This compound, however, was different from our β-keto ester **10**, since it appeared to be fully enolized, and it had a carbonyl oxygen rather than a *tert*-butyl ether function at the C-1 position.

It has also been reported, after the conclusion of our experimental work, that hydrogenation of the above-mentioned fully enolized β-keto ester gives, even without copper chelate formation, the desired C/D trans β-keto ester, although in a considerably lower (64%) yield.[15]

It has also been known that hydrogenation of a $\Delta^{14(15)}$ double bond (steroidal numbering) in a BCD tricyclic derivative with an aromatic B ring and a 17-hydroxyl group yields the desired C/D trans-fused system.[16] The analogy with the hydrogenation of the pseudo B ring containing β-keto esters is apparent.

It should finally be pointed out that, although the trans β-keto ester **13** did not give a ferric chloride test to indicate enolization, its sodium enolate could be formed with 0.01 *N* sodium methoxide in methanol at room temperature, as indicated by uv spectroscopy [λ_{max} 275 nm (ε 13,050)]. This was important in view of the desire to use this compound as a building block in a steroid total synthesis. The results of this investigation will be the topic of the accompanying publication.[17]

Experimental Section[18]

(±)-3aβ,4,7,7a-Tetrahydro-1β-hydroxy-7aβ-methyl-5(6*H*)-indanone (2).—Catalytic hydrogenation of **1a** (1.66 g) was carried out in the presence of 0.2 g of 5% Pd/$CaCO_3$ in 50 ml of absolute ethanol at 1 atm pressure and 23°. Hydrogen uptake ceased after 45 min. The solution was filtered and evaporated *in vacuo* to give 1.63 g (97%) of the crude cis hydrogenation product, mp 81–90°, 88.5% pure by vpc. An analytical sample was prepared by preparative tlc and recrystallization from petroleum ether (bp 60–70°), followed by sublimation at 90° (0.015 mm): mp 93.5–95°; ir 3620, 3350–3550 (OH), and 1712 cm^{-1} (C=O); nmr δ 1.17 (s, 3, 7aβ-CH_3), 2.20 (s, OH), and 3.86 ppm (t, $J_{1H,2H}$ = 4.5 Hz, CHOH).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.46; H, 9.44.

General Procedure for the Catalytic Hydrogenation of 1b.—Hydrogenations were carried out at 1 atm pressure and 20° with a 0.5% solution of **1b** using a 1:10 catalyst to substrate ratio. Hydrogenation was stopped after the uptake of 1 mol of hydrogen and the solution was filtered and evaporated *in vacuo*. The crude hydrogenation product was subjected to hydrolysis (*cf.* Table I).

General Procedure for the Hydrolysis to the Cis (2) and Trans (3) Reduction Products.—The crude hydrogenation product was stirred and refluxed for 6 hr with a 1:1 mixture of tetrahydrofuran and 2 *N* aqueous HCl under nitrogen. It was cooled in an ice bath and neutralized with 5 *N* aqueous NaOH, and the solvent was evaporated *in vacuo*. The residue was extracted with ethyl acetate and with ether. The combined extract was washed with a saturated aqueous NaCl solution and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave a mixture of **2** and **3**, which was analyzed by vpc and nmr (*cf.* Table I).

(±)-3aα,4,7,7a-Tetrahydro-1β-hydroxy-7aβ-methyl-5(6*H*)-indanone (3). A. From the Bicyclic *tert*-Butyl Ether 1b.—Hydrogenation of **1b** (5.0 g) in *n*-hexane with 5% Pd/C catalyst followed by hydrolysis gave 3.48 g of a mixture of **2** and **3**. This was repeatedly subjected to vapor phase chromatography in 40-mg portions on a Barber-Coleman Model 5072 instrument with flame detection and a split ratio of 5:95. The column was a 4 ft × 12 mm (i.d.) glass column with 20% Carbowax 20M on 60–80 mesh Chromosorb P. Nitrogen flow was 200 cc/min and the temperature was held at 200°. By this technique 0.22 g (6.3%) of **3** (96% pure by analytical vpc) was obtained as an oil: ir 3620 (OH), 3300–3550 (associated OH), and 1715 cm^{-1} (C=O); nmr δ 1.02 (s, 3, 7aβ-CH_3), 2.28 (s, 1, OH), and 3.78 ppm (t, $J_{1H,2H}$ = 4.5 Hz, CHOH).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.11, H, 9.32.

B. From the Trans Bicyclic β-Keto Acid 8.—Compound **8** (1.34 g of 93.7% purity) was hydrolyzed and decarboxylated by heating it at reflux under nitrogen for 6 hr in a mixture of 2.5 ml of tetrahydrofuran and 2.5 ml of 2 *N* aqueous HCl. The solution was neutralized with 2 *N* aqueous NaOH and evaporated *in vacuo*. The residue was extracted with ether, and the extract was washed with a small amount of saturated aqueous NaCl solution, dried (Na_2SO_4), and evaporated *in vacuo* to give 838 mg of the trans keto alcohol **3** as a waxy solid, mp 41–42°. The compound was shown by ir and nmr to be identical with the sample described under A.

C. From the Hydroxy β-Keto Acid 9.—The trans compound **9** (17.3 mg) was decarboxylated by heating it at reflux in 1.5 ml of toluene for 30 min under nitrogen. The solvent was evaporated *in vacuo* to give 13.7 mg of **3** (95.5% pure by vpc), which was identified by ir and nmr spectroscopy.

(±)-3aα,4β,5,6,7,7a-Hexahydro-1β-hydroxy-7aβ-methyl-5-oxo-4a-indancarboxylic Acid (9).—The trans β-keto acid **8** (246 mg) was suspended in 6 ml of concentrated HCl and stirred for 24 hr under nitrogen at 20°. The resulting solution was evaporated *in vacuo* at 30° to give a crude solid. This was triturated with ether to give 182 mg (93%) of the hydroxy β-keto acid **9**, mp 102–104° dec. Recrystallization from ether gave 112.5 mg of analytically pure **9**: mp 123° dec; ir (KBr) 3350 and 2500–2750 (OH), 1730 (C=O of acid), and 1700 cm^{-1} (C=O); nmr (acetone) δ 1.09 (s, 3, 7aβ-CH_3) and 3.38 ppm (d, $J_{3aH,4H}$ = 13 Hz, -CHCOOH).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.44; H, 7.40.

(±)-3aα,4,7,7a-Tetrahydro-7aβ-methyl-1,5(6*H*)-indandione (5).—The trans keto alcohol **3** (250 mg) was dissolved in 15 ml of acetone and oxidized with 0.48 ml of 8.0 *N* CrO_3–H_2SO_4 while stirring at 0° for 10 min. The reaction was quenched with 30 ml of ice–water, and the solvent was evaporated *in vacuo*. The residue was extracted with ethyl acetate, and the extract was washed with $NaHCO_3$ and NaCl solution, dried (Na_2SO_4), and evaporated *in vacuo* to give an oily crude product.

A. Isolation of 5 by Preparative Tlc.—Preparative tlc of this crude product on 8 in. × 8 in. × 1 mm thick silica gel plates with

(14) G. Stork, private communication.

(15) G. Nominé, G. Amiard, and V. Torelli, *Bull. Soc. Chim. Fr.*, 3664 (1968).

(16) D. K. Banerjee, S. Chatterjee, C. N. Pillai, and M. V. Bhatt, *J. Amer. Chem. Soc.*, **78**, 3769 (1956).

(17) Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, **38**, 3244 (1973).

(18) All melting points were determined in a Thomas-Hoover melting point apparatus and are corrected; unless otherwise noted all uv spectra were taken in ethyl alcohol; ir spectra were taken in absolute chloroform; nmr spectra were taken in $CDCl_3$ on a Varian A-60 or HA-100 spectrometer with tetramethylsilane as an internal standard; analytical vpc was performed on an F & M Model 810 instrument in the flame mode using a 6 ft × 0.25 in. aluminum column with 1% PEG 4000 MA on 60–70 mesh Anakrom ABS with nitrogen flow of 100 cc/min and programmed temperature.

1:1 benzene–ethyl acetate gave 210 mg of the desired crystalline material **5**. Crystallization from a small amount of ether gave 131 mg of pure **5**: mp 52.5–53° (lit.[2b] mp 52–53°); ir 1740 (five-ring C=O), and 1712 cm^{-1} (six-ring C=O); nmr, *cf.* Table II.

B. Isolation of 5 by Preparative Vpc.—The crude oxidation product (68 mg) was subjected to preparative vpc in 14-mg aliquots on a Barber-Coleman Model 5072 instrument with flame detection and a split ratio of 5:95. The column was a 6 ft × 6 mm (i.d.) glass column with 2% Carbowax 20M + 2% KOH on 20–30 mesh Chromosorb A. Nitrogen flow was 200 cc/min; temperature was held at 170°. Fractionation gave 43 mg (63%) of **5**. The compound was shown by ir and nmr to be identical with the sample described under A.

(±)-1β-*tert*-Butoxy-5,6,7,7a-tetrahydro-7aβ-methyl-5-oxo-4-indancarboxylic Acid (7).—To a 53% dispersion of NaH in mineral oil (1.03 g), which had been washed with anhydrous ether and dried under nitrogen, was added 45 ml of DMSO (distilled from calcium hydride). The mixture was stirred at 20°, and a solution of the enone **1b** (5.0 g) in 45 ml of dry DMSO was added at once. The mixture was stirred under nitrogen until hydrogen evolution ceased (*ca.* 4 hr). The DMSO was then distilled under high vacuum with a 75° bath. The residue (conjugate anion of **1b**) was dissolved in 90 ml of anhydrous ether, and added as rapidly as possible (*ca.* 2 min) to a 1-l. flask containing a thick slurry of anhydrous solid CO_2 stirred in 225 ml of anhydrous ether. The reaction mixture was rapidly stirred for 6 hr with a Dry Ice–methanol cooling bath and was then allowed to stand at 20° for 16 hr. The ethereal solution was extracted with 250 ml of 0.02 *N* aqueous NaOH while stirring under nitrogen for 1 hr. The aqueous layer was separated, and the ether layer was washed two more times with water. The ethereal solution was dried (Na_2SO_4) and evaporated *in vacuo* to give 3.14 g (62.8%) of unchanged starting material (**1b**). The aqueous solution was filtered from a small amount of impurity and was then carefully acidified at ice-bath temperature with 2 *N* aqueous HCl to pH 2.5. It was then extracted two times with benzene and once with ether. The combined extract was washed with saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give 2.14 g (35.8%) of the unsaturated bicyclic β-keto acid **7** as a dry solid, mp 153–160° dec. An analytically pure sample of **7** was obtained by crystallization from acetone: mp 159.5° dec; uv 249 nm (ε 9800); ir, *cf.* discussion; nmr δ 1.20 ppm [s, 12, $-C(CH_3)_3$ and 7aβ-CH_3].

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.63; H, 8.62.

(±)-1β-*tert*-Butoxy-3aα,4β,5,6,7,7a-hexahydro-7aβ-methyl-5-oxo-4-indancarboxylic Acid (8).—The unsaturated β-keto acid **7** (1.84 g) was dissolved in 92 ml of ethanol and hydrogenated in the presence of 184 mg of 10% Pd/$BaSO_4$ at 1 atm pressure and 20°. The theoretical amount of hydrogen was taken up in 20 min. The solution was filtered and evaporated *in vacuo* to give 1.81 g (97.9%) of **8**, mp 107.5–109° dec. Vpc indicated a 93.7% trans and 5.1% cis isomer ratio. This grade of compound was used in subsequent operations. An analytically pure sample of **7** was obtained by crystallization from ether: mp 114–114.5° dec; ir (10% piperidine in absolute $CHCl_3$) 1705 (C=O) and 1630, 1585, and 1390 cm^{-1} (COO^-); nmr δ 1.03 (s, 3, 7aβ-CH_3), 1.15 [s, 9, $-C(CH_3)_3$], and 3.38 ppm (d, $J_{3aH,4H}$ = 13 Hz, –CHCOOH).

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 66.95; H, 9.09.

(±)-1β-*tert*-Butoxy-5,6,6,7a-tetrahydro-7aβ-methyl-5-oxo-4-indancarboxylic Acid Methyl Ester (10).—The unsaturated β-keto acid **7** (134 mg) was suspended in 5 ml of ether. The suspension was cooled to 0°, and 7.6 ml of a diazomethane solution in ether (0.076 mmol/ml) was added dropwise with stirring. After 10 min the solution was evaporated *in vacuo* to give 141 mg (99.4%) of the methyl ester **10**, mp 73–76°. Crystallization from petroleum ether (bp 30–60°) gave analytically pure **10**: mp 76.5–77°; uv 240 nm (ε 10,500); ir 1735 (ester C=O) and 1675 cm^{-1} (unsaturated C=O); nmr δ 1.17 (s, 3, 7aβ-CH_3), 1.18 [s, 9, $-C(CH_3)_3$], and 3.80 ppm (s, 3, CO_2CH_3).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.41; H, 8.92.

(±)-1β-*tert*-Butoxy-3aα,4β,5,6,7,7a-hexahydro-7aβ-methyl-5-oxo-4α-indancarboxylic Acid Methyl Ester (13). A. From the Trans β-Keto Acid 8.—Compound **8** (50 mg) was dissolved in 1.0 ml of ether. The solution was cooled to 0°, and 1.05 ml of a solution of diazomethane in ether (0.19 mmol/ml) was added dropwise with stirring. After 15 min the solution was evaporated *in vacuo* to give 52.2 mg (99.2%) of the β-keto ester **13**, mp 112.5–113.5°. Crystallization from ether–petroleum ether gave analytically pure **13**: ir 1743 (ester C=O) and 1710 cm^{-1} (C=O); nmr δ 0.99 (s, 3, 7aβ-CH_3), 1.12 [s, 9, $-C(CH_3)_3$], 3.34 (d, $J_{3aH,4H}$ = 13 Hz, $-CHCO_2CH_3$), and 3.69 ppm (s, 3, CO_2CH_3).

Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.03; H, 9.28. Found: C, 68.09; H, 9.49.

B. By the Catalytic Hydrogenation of 10.—The bicyclic unsaturated β-keto ester **10** (54.4 mg) was dissolved in 2.7 ml of absolute ethyl alcohol, and hydrogenated in the presence of 18.2 mg of 10% Pd/$BaSO_4$ catalyst at 1 atm pressure and 21°. Hydrogen uptake ceased after 15 min. The solution was filtered and evaporated *in vacuo* to give 56 mg of a crude mixture (**12** and **13**, as indicated by uv and ir spectroscopy). A sample after standing at 20° for 16 hr had mp 104–109° and ir and nmr spectra which were superimposable with those of an authentic sample of **13** prepared from **8** (*cf.* also discussion).

Acknowledgment.—The authors wish to express their thanks to Mr. Fred Bizzarro for his technical assistance in this investigation. Thanks are due to Dr. T. Williams for the nmr, to Dr. V. Toome for the uv, to Mr. S. Traiman for the ir spectroscopic data, to Dr. A. Steyermark for the microanalyses, and to Mr. H. Jenny for the vpc results.

Registry No.—**1a**, 17553-80-9; **1b**, 39765-89-4; **2**, 40682-65-3; **3**, 27504-54-7; **4**, 25222-16-6; **5**, 33205-64-0; **7**, 27510-27-6; **8**, 27504-53-6; **9**, 27801-96-3; **10**, 27504-57-0; **13**, 27504-58-1.

Stereocontrolled Total Synthesis of 19-Nor Steroids

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Received February 15, 1973

The C/D trans bicyclic β-keto ester **1** (electron donor) and ethyl vinyl ketone **2** (electron acceptor) model system gave the BCD-tricyclic **6** with the undesired stereochemistry at the steroidal C-8 position. Converting **1** to the electron acceptor β-keto mesylate **11** and attacking this with the anion of the β-keto ester **12** gave the desired BCD intermediate, (±)-**16**. The new synthetic scheme lends itself to the direct preparation of C-6-substituted derivatives (*e.g.*, **15**). Alternatively, the C/D trans bicyclic β-keto acid **17** could be converted to the α-methylene ketone **19**. An attack on this electron acceptor with the anion of **12** gave (±)-17β-hydroxy-$\Delta^{9(10)}$-de-*A*-androsten-5-one, (±)-**7**, in a two-step synthesis. Attacking **19** with the anion of a long-chain β-keto ester **20** gave (±)-19-nortestosterone, (±)-**21**, in a five-step stereocontrolled synthesis involving a single annulation reaction.

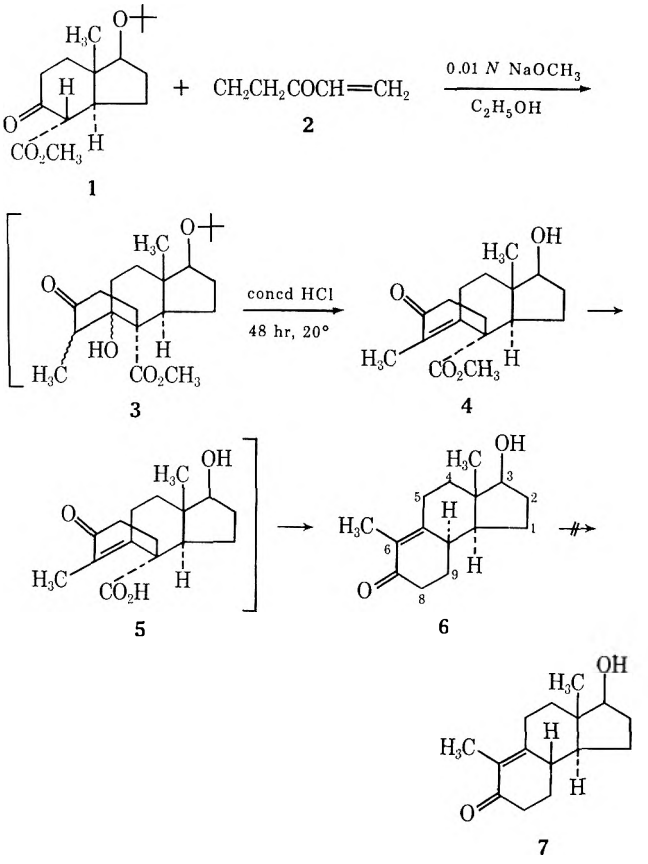
The total synthesis of steroids in general and of 19-nor steroids in particular has been quite extensively explored during the past approximately 35 years.[2]

In planning a new scheme of the total synthesis of 19-nor steroids it was contemplated to construct a properly functionalized bicyclic intermediate with the desired C/D trans stereochemistry, and then elaborate and attach ring B or rings A and B in a stereocontrolled single annulation reaction. The first problem has been the topic of the preceding communication;[3] the second part of the problem constitutes the subject matter of the present discussion.

In the first synthetic approach it was planned to use the C/D trans bicyclic β-keto ester **1**[3] as an electron donor and an α,β-unsaturated ketone such as ethyl vinyl ketone (**2**) as an electron acceptor in a model reaction. It was most important to find out if the desired stereochemistry could be obtained at C-8 and maintained at C-14 (steroidal numbering) during the course of the synthetic operation. The BCD-tricyclic intermediate (±)-**7** with the proper stereochemistry has been available to us for comparison by two independent syntheses in these laboratories.[4]

Since we have shown that the sodium enolate of the β-keto ester **1** can be formed with 0.01 *N* sodium methoxide in methanol,[3] the addition reaction to ethyl vinyl ketone **2** has been carried out in the presence of a catalytic amount of this base in methanol. Attempts to decarboxylate the reaction product **3** (Scheme I) under conditions normally used for β-keto esters were unsuccessful, suggesting the indicated ketol ester type of structure. Only after the elimination of water from **3** with concentrated hydrochloric acid could the vinylogous β-keto ester **4** be converted into a BCD tricyclic ketone **6** *via* hydrolysis to **5** followed by decarboxylation. The compound **6** proved to be different from the desired tricyclic racemic compound (±)-**7** by uv and ir spectroscopy and also by vpc analysis.

SCHEME I[a]



[a] All compounds reported in this paper are racemic; for convenience, only one enantiomer is shown.

The tricyclic derivative **6** is most likely a 9a-α isomer, formed by an sp^3-hybridized transition state in the decarboxylation reaction.[5] It could not be equilibrated to the desired (±)-**7**. There is presumably strong preference to involve the C-5 rather than the C-9a position in the conjugate anion formation, because of the C/D trans ring junction.[6]

There are probably two reasons for obtaining the wrong isomer: (a) the alkylation reaction proceeds in agreement with the *axial* alkylation principle[6,7] and (b) the initially formed alkylation product closes to the ketol ester intermediate **3**, thereby fixing the undesired stereochemistry of the B/C ring junction.

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(2) (a) For leading references up to 1966 see L. Velluz, J. Mathieu, and G. Nomine, *Tetrahedron, Suppl. 8, Part II*, 495 (1966). (b) P. Crabbe in "Terpenoids and Steroids," Vol. 2, K. H. Overton, Senior Reporter, The Chemical Society, London, 1972, p 329. (c) P. J. May in "Terpenoids and Steroids," Vol. 1, K. H. Overton, Senior Reporter, The Chemical Society, London, 1971, p 468. (d) S. E. Danishefsky and S. Danishefsky in "Progress in Total Synthesis," Vol. 1, Appleton-Century-Crofts, New York, N. Y., 1971, p 242. (e) A. A. Akhrem and Y. A. Titov, "Total Steroid Synthesis," Plenum Press, New York, N. Y., 1970.

(3) Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, **38**, 3239 (1973).

(4) (a) Z. G. Hajos, R. A. Micheli, D. R. Parrish, and E. P. Oliveto, *J. Org. Chem.*, **32**, 3008 (1967); (b) G. Saucy, R. Borer, and A. Fürst, *Helv. Chim. Acta*, **54**, 2034 (1971).

(5) J. P. Ferris and N. C. Miller, *J. Amer. Chem. Soc.*, **88**, 3522 (1966).

(6) L. Velluz, J. Valls, and G. Nomine, *Angew. Chem.*, **77**, 185 (1965).

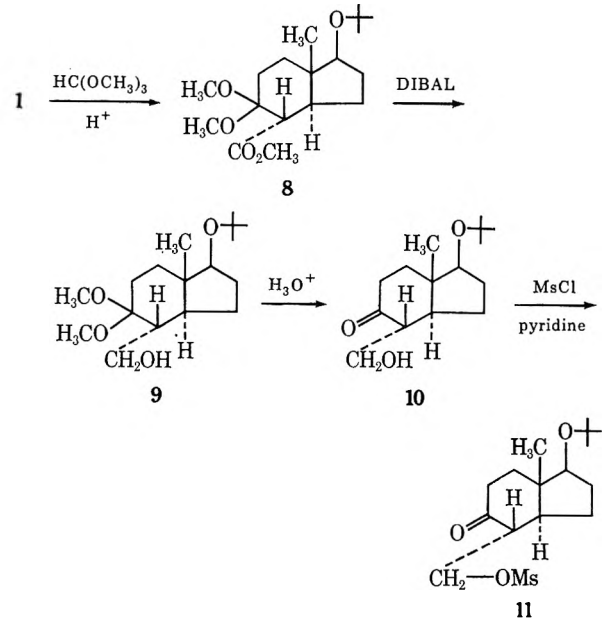
(7) T. A. Spencer, T. D. Weaver, R. M. Villarica, R. J. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968).

On the other hand, the total synthesis of (±)-8β-methoxycarbonylestrone 3-methyl ether from 4α-methoxycarbonyl-7aβ-methyl-3aα-perhydroindene-1,5-dione and vinylcyclohexenone has been recently reported.[8] Structural differences of this Michael acceptor in comparison with ethyl vinyl ketone may well explain the different steric course of this synthesis.

In view of the results with ethyl vinyl ketone we decided to try to use the CD bicyclic compound as an electron acceptor rather than electron donor moiety in a synthesis which would allow the introduction of the proper stereochemistry at C-8 (steroidal numbering). Based on this idea we have indeed worked out two synthetic routes, one *via* the β-keto mesylate **11** and another *via* the α-methylene ketone **19**, leading to compounds possessing the desired stereochemistry.

The C/D trans bicyclic β-keto ester **1** was converted in a four-step sequence involving ketalization, reduction, hydrolysis, and mesylation to the β-keto mesylate **11** in an 87% overall yield (Scheme II). This β-keto

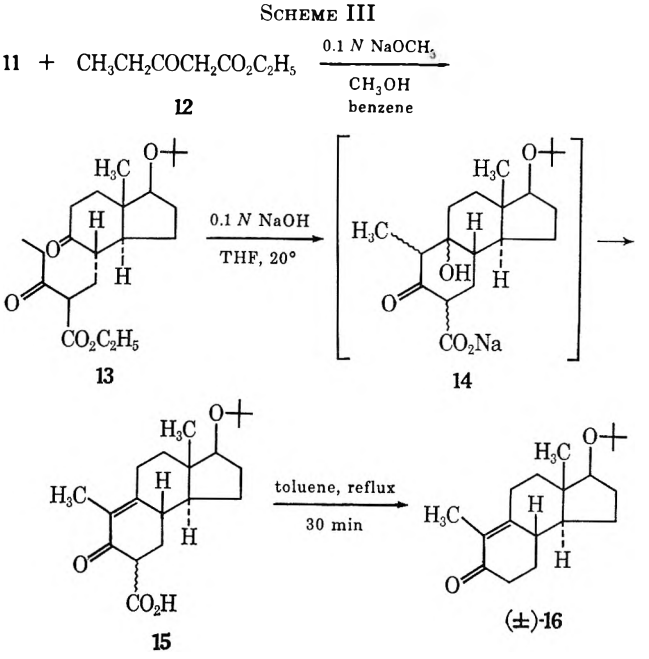
Scheme II



mesylate was then allowed to react with the anion of ethyl propionyl acetate (**12**) to give the diketo ester **13**. The side chain of **13** assumed the thermodynamically favorable α equatorial orientation. This was due to the presence of an enolizable proton at the C-8 position (steroidal numbering). No ring closure occurred at this stage, because of the preferred enolization of the side-chain keto group toward the carboxylic ester function. Saponification of the ester group of **13** allowed ring closure to a nonisolated ketol (**14**) which was dehydrated to the α,β-unsaturated β-keto acid **15** by careful acidification of the reaction mixture. Decarboxylation in refluxing toluene gave the crude BCD tricyclic intermediate (±)-**16** (Scheme III). The structure was confirmed and the purity of the sample was established by comparing the uv, ir, tlc, and vpc data of the sample with those of an optically active sample

(8) K. Sakai and S. Amemiya, *Chem. Pharm. Bull.*, **18**, 641 (1970).

Scheme III



of **16**.[9] This then constitutes chemical evidence of the stereochemistry of the bicyclic intermediate by connecting it with a BCD tricyclic derivative of known steric arrangement.

It should be pointed out that the carboxylic acid group in **15** is at the steroidal C-6 position. The metabolic role of a substituent at C-6 is well known.[2a] The new synthetic scheme thus lends itself to the preparation of such C-6 substituted derivatives.

Next we considered means of simplifying and improving the above-described synthesis. It was hoped that the trans bicyclic β-keto acid **17** could be converted to a β-amino ketone **18** in a Mannich reaction. The β-amino ketone in turn could be used in place of the β-keto mesylate **11** in the modified scheme. The β-keto acid **17**, however, suffered extensive decarboxylation in the presence of aqueous formaldehyde and piperidine hydrochloride. The desired reaction product could therefore not be obtained. It should be mentioned that these were essentially the conditions used by Mannich[10] to prepare β-amino ketones from β-keto acids, and by Robinson[11] and Schöpf[12] in their tropinone syntheses.

It occurred to us that decarboxylation of the β-keto acid **17** might lead to an intermediate $\Delta^{8(9)}$-enol (steroidal numbering), which could immediately be quenched by the formaldehyde–piperidine system, if the proper solvent was used. We chose to try dimethyl sulfoxide, because it was known to promote the decarboxylation of vinylogous β-keto acids.[13] The β-keto acid **17** was therefore dissolved in dimethyl sulfoxide, and the solution was allowed to stand at room temperature. Considerable decarboxylation occurred after a period of 2 hr, as indicated by thin layer chromatography. The β-keto acid **17** was then allowed to react with aqueous formaldehyde and piperidine hydrochloride in dimethyl sulfoxide at room temperature, giving

(9) Obtained through the courtesy of Dr. R. A. Micheli of these laboratories.

(10) C. Mannich and M. Bauroth, *Chem. Ber.*, **57**, 1108 (1924).

(11) R. Robinson, *J. Chem. Soc.*, **111**, 766 (1917).

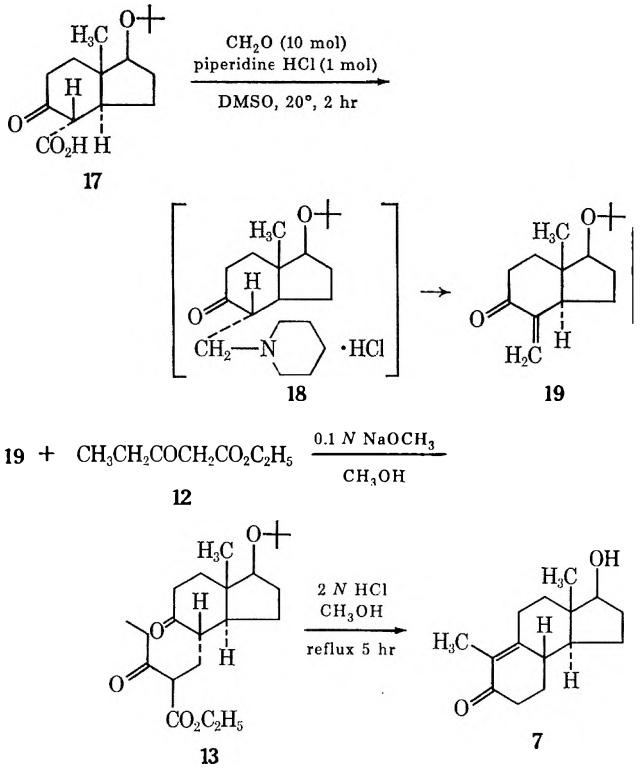
(12) C. Schöpf and G. Lehmann, *Justus Liebigs Ann. Chem.*, **518**, 1 (1935).

(13) K. Tanabe, R. Takasaki, R. Hayashi, and Y. Morisawa, Excerpta Medica No. 111, Second International Congress on Hormonal Steroids, 1966, p 191.

the α-methylene ketone **19** in excellent yield. The expected intermediate **18** was most likely formed, but it lost piperidine hydrochloride in the highly polar reaction medium. Although the crude, unpurified α-methylene ketone **19** can be used in the total synthesis, a sample of it was purified by preparative thin layer chromatography, and its structure was verified by uv, ir, nmr, and low-resolution mass spectrometry.

Michael addition of the anion of ethyl propionyl acetate (**12**) to **19** gave the diketo ester **13** (Scheme IV).

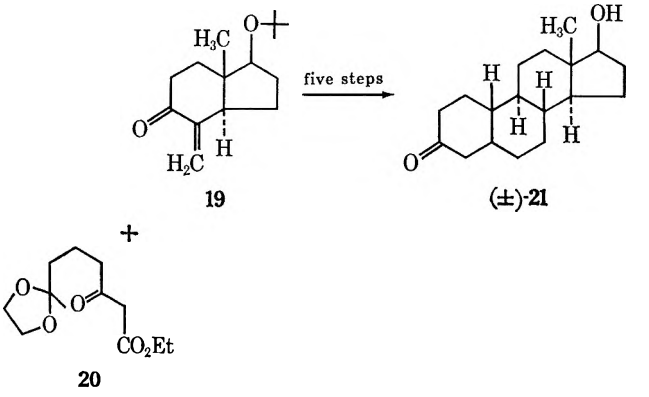
SCHEME IV



The compound was identical by ir spectroscopy and tlc with the sample obtained from the β-keto mesylate **11** (Scheme III). The addition most likely involved formation of the $\Delta^{8(9)}$-enol, followed by ketonization. Protonation at C-8 (steroidal numbering) must have occurred from the preferred axial direction,[6] thereby placing the side chain of **13** in the stereochemically desired equatorial configuration. No ring closure occurred at this stage for reasons already explained during the discussion of Scheme III. Hydrolysis of the *tert*-butyl ether and of the β-keto ester groups with refluxing hydrochloric acid in methanol, on the other hand, was accompanied by ring closure, dehydration, and decarboxylation to give the desired racemic BCD tricyclic intermediate (±)-**7**. The compound was in all respects identical with a sample obtained by an independent route.[4a] It may also be mentioned that the corresponding optically active derivative (−)-**7** has also been described in the literature.[14,15]

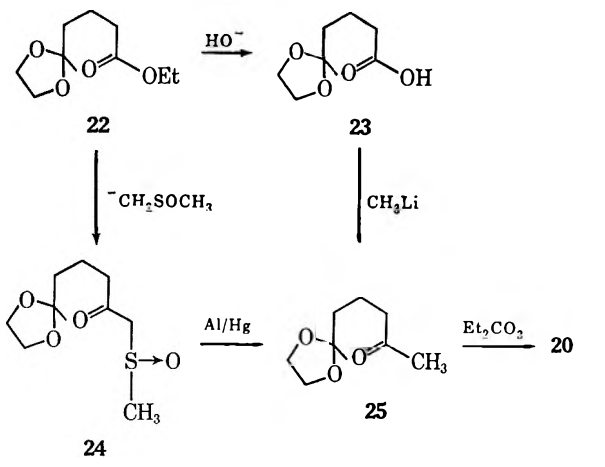
After having realized the above-described results we were ready to adapt our scheme to the preparation of 19-nor steroids. The strategy of the synthesis involved the addition of an A–B (fragment) building block, the β-keto ester **20**, to a B (fragment)–CD building block, the bicyclic trans α methylene ketone **19**, to give in a five-step stereocontrolled synthesis racemic 19-nortestostereone (±)-**21** or the optically active 19-nor steroid, if optically active **19** were used in the synthesis. Rings A and B are thus constructed in a single annulation reaction (Scheme V).

SCHEME V



The β-keto ester **20** was prepared by two routes (Scheme VI) starting with the known[16] ketal ester **22**.

SCHEME VI



This compound (**22**) was allowed to react with methylsulfinyl carbanion[17] to give the β-keto sulfoxide **24**. Reduction with aluminum amalgam gave the ketal ketone **25**. This compound has been previously obtained by an independent synthesis.[18] Alternatively, the ketal ester **22** could be saponified to the known[19] ketal acid **23** and the latter converted to the ketal ketone **25** with methyllithium. Carbethoxylation at the terminal carbon atom[20] of the anion of **25** gave the desired β-keto ester **20**, the A–B (fragment) building block.

Michael addition of this compound (**20**) to the crude α-methylene ketone **19** gave the diketo ester **26**. This

(14) Roussel-Uclaf, French Patent 1,359,657 (1963); L. Velluz, G. Nominé, G. Amiard, V. Torelli, and J. Cérède, *C. R. Acad. Sci.*, **257**, 3086 (1963).

(15) (a) Z. G. Hajos, D. R. Parrish, and E. P. Oliveto, *Tetrahedron*. **24**, 2039 (1968); (b) G. Saucy and R. Borer, *Helv. Chim. Acta*, **54**, 2121(1971).

(16) R. I. Meltzer, A. D. Lewis, J. Volpe, and D. M. Lustgarten, *J. Org. Chem.*, **25**, 712 (1960).

(17) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **86**, 1639 (1964).

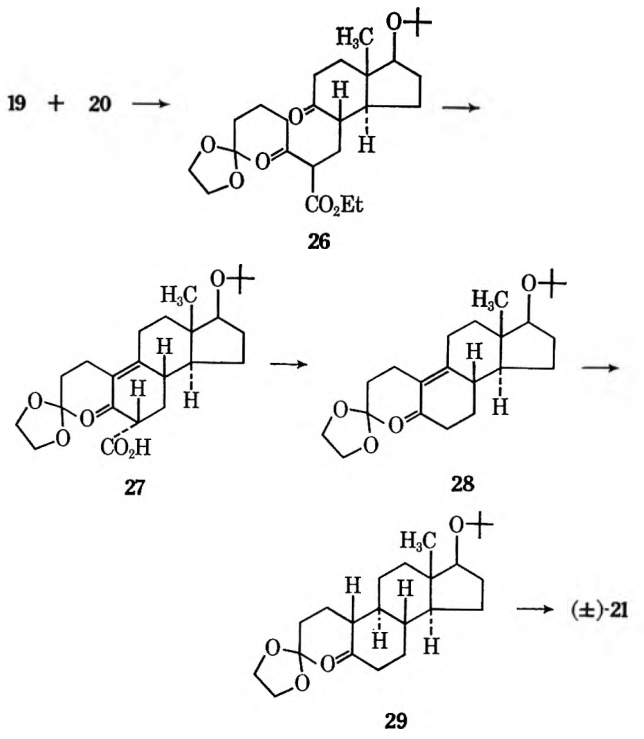
(18) C. Feugeas, *Bull. Soc. Chim. Fr.*, 2568 (1963).

(19) R. A. LeMahieu, *J. Org. Chem.*, **32**, 4149 (1967).

(20) S. B. Soloway and F. B. LaForge, *J. Amer. Chem. Soc.*, **69**, 2677 (1947).

was then converted to the unsaturated keto acid **27** *via* saponification of the ester group followed by ring closure and dehydration (Scheme VII). Nmr spectros-

SCHEME VII



copy of **27** indicated an equatorial carboxyl group (quartet centered at δ 3.33, C-6 hydrogen; $J_{6H,7eH}$ = 4.5, $J_{6H,7aH}$ = 14.5 Hz).

Decarboxylation of the crude β-keto acid **27** in refluxing toluene gave the enone **28**.[21] It should be mentioned that under carefully controlled reaction conditions it is possible to maintain the carboxylic acid or the carboxylic ester group to the very end of the total synthesis, and thus obtain C-6 substituted 19-nor steroids.[22] Catalytic hydrogenation of the $\Delta^{9(10)}$ double bond of **28** gave intermediate **29** with the desired 9α,10β configuration. It should be mentioned that intermediates **27**, **28**, and **29** could be purified by trituration and crystallization. During the course of the total synthesis, however, this was not necessary, and only the final product was purified by the appropriate method.

Hydrolysis of the *tert*-butyl ether group and of the protective cyclic ethylene ketal group as well as ring closure and dehydration could be achieved by refluxing crude **29** with hydrochloric acid in methanol to give racemic 19-nortestosterone [(±)-**21**], which could be purified by crystallization or by chromatography. The uv, ir, nmr, and tlc data of (±)-**21** obtained by this synthesis were in agreement with those of an optically active authentic sample [(+)-**21**].[23]

It may be mentioned that the desired bicyclic optically active enantiomer (+)-(1*S*,7a*S*)-7,7a-dihydro-1-hydroxy-7a-methyl-5(6*H*)-indanone is available both through conventional chemical resolution[15a] and also through asymmetric synthesis.[24] With this starting material the synthesis of the desired optical isomer of the α-methylene ketone **19** as well as of 19-nortestosterone **21** and of other optically active 19-nor steroids can now be realized.

Experimental Section[25]

Alkylation of the β-Keto Ester 1[3] with Ethyl Vinyl Ketone.—The β-keto ester **1** (54.0 mg) was dissolved in 1.8 ml of absolute ethyl alcohol, and 0.05 ml of 1 *N* sodium ethoxide in ethanol was added. The solution was stirred for 10 min at 20° under nitrogen, and 0.33 ml of a solution of ethyl vinyl ketone (1 ml) in ethyl alcohol (10 ml) was added after which the solution was allowed to stand at 20° for 72 hr. The resulting mixture showed no starting material by tlc; it showed a major reaction product with an R_f of 0.53 (silica gel, 80% benzene, 20% ethyl acetate) which had no absorption in the uv. Concentrated HCl (0.8 ml) was added to one half of the preparation, and it was allowed to stand at 20° for 48 hr. The reaction mixture was extracted with ether. The extract was washed with saturated $NaHCO_3$ and NaCl solutions, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give 6.5 mg of **6** as an oil: uv 243 nm (ϵ 8950); ir 3620 (unassociated OH), 3200–3560 (associated OH), 1715 (saturated keto impurity), and 1655 cm^{-1} (α,β-unsaturated ketone). Thin layer chromatography showed a major uv-absorbent and a minor uv-nonabsorbent component. The uv-absorbent spot was slightly slower than that of (±)-**7**. Vpc showed one major component (73.8%) with a retention time of 19.9 min. Retention time for (±)-**7** was 17.4 min.

(±)-1β-*tert*-Butoxy-3aα,4β,5,6,7,7a-hexahydro-5,5-dimethoxy-7aβ-methyl-4α-indancarboxylic Acid Methyl Ester (8).—The β-keto ester **1** (141 mg) was dissolved in a mixture of 1.25 ml of methanol and 0.55 ml of trimethyl orthoformate. The solution was cooled in an ice bath to 0°, and 0.26 ml of 2 *N* methylsulfuric acid was added with stirring under nitrogen. After 5 min at 0° the mixture was allowed to stand at 20° for 16 hr. It was cooled with an ice bath and neutralized with 1 *N* $NaOCH_3$. The solvent was evaporated *in vacuo*, and the residue was extracted with ether. The extract was washed with aqueous $NaHCO_3$ and NaCl solution, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give 160 mg (97.5%) of **8** as an oil, ir 1728 cm^{-1} (ester carbonyl).

(±)-1β-*tert*-Butoxy-3aα,4β,5,6,7,7a-hexahydro-5,5-dimethoxy-7aβ-methyl-4-indanmethanol (9).—The ketal ester **8** (160 mg) was dissolved in 3.5 ml of dry toluene. The solution was cooled to 0°, and 4.5 ml of a 20% solution of diisobutylaluminum hydride in toluene was added within 5 min with stirring under nitrogen. After an additional 30 min at 0° the mixture was allowed to stand at 20° for 16 hr. It was then cooled with an ice bath, and 3.0 ml of methanol was added carefully with stirring. After 10 min at 0° it was stirred at 20° for 1 hr. The crystalline precipitate was filtered through a pad of Celite, and it was washed and extracted thoroughly with ethyl acetate. The filtrate was washed with saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give 131.6 mg (90%) of **9** as an oil, ir 3575 cm^{-1} (unassociated OH).

(±)-1β-*tert*-Butoxy-3aα,4β,5,6,7,7a-hexahydro-7aβ-methyl-5-oxo-4-indanmethanol (10).—The ketal alcohol **9** (31.6 mg) was dissolved in 1.8 ml of acetone. The solution was cooled to 5°, and 0.2 ml of distilled water and 0.03 ml of 2 *N* HCl were added with stirring. After 20 min the solution was neutralized with 0.065 ml of saturated $NaHCO_3$ solution. Acetone was evaporated *in vacuo*, and the residue was extracted with ether. The extract was washed with a saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give 30.2 mg (99.2%) of **10** as an oil, ir 3580 (unassociated OH) and 1695 cm^{-1} (keto carbonyl).

(±)-1β-*tert*-Butoxy-3aα,4β,5,6,7,7a-hexahydro-7aβ-methyl-5-

(21) C. A. Henrick, E. Böhme, J. A. Edwards, and J. H. Fried, *J. Amer. Chem. Soc.*, **90**, 5926 (1968), report the presence of optically active **28** in a reaction mixture obtained by an independent route, but the pure compound has not been described in the paper.

(22) Z. G. Hajos, U. S. Patent 3,692,803 (Sept 19, 1972).

(23) This sample was obtained from Organon, Inc., West Orange, N. J.

(24) Z. G. Hajos and D. R. Parrish, forthcoming publication.

(25) All melting points were determined in a Thomas-Hoover melting point apparatus and are corrected; unless otherwise noted all uv spectra were taken in ethyl alcohol; ir spectra were taken in chloroform; nmr spectra were taken in $CDCl_3$ on Varian A-60 or HA-100 spectrometers with tetramethylsilane as an internal standard; analytical vpc was performed on a F & M Model 810 in the flame mode using a 6 ft × 0.25 in. aluminum column with 1% PEG 4000MS on 60–70 mesh Anakrom ABS with nitrogen flow of 100 ml/min and programmed temperature.

oxo-4-indanmethanol Methanesulfonate (11).—The β-keto alcohol 10 (17.4 mg), dissolved in 0.25 ml of dry pyridine, was cooled to 0°. Methanesulfonyl chloride (8.0 mg) in 0.56 ml of dry pyridine was added while stirring. The reaction mixture was then allowed to stand at 20° for 1.5 hr. It was evaporated to dryness *in vacuo*, and the residue was dissolved in chloroform and washed with water and a saturated NaCl solution. It was dried ($NaSO_4$), filtered, and evaporated *in vacuo* to give 24.1 mg of 11 as an oil, ir 1705 (keto carbonyl), 1353, and 1175 cm^{-1} (sulfonate).

(±)-2-(1β-*tert*-Butoxy-3aα,4β,5,6,7,7a-hexahydro-7aβ-methyl-5-oxo-4-indanylmethyl)-3-oxovaleric Acid Ethyl Ester (13).—The β-keto mesylate 11 (22.9 mg) was dissolved in a mixture of 0.3 ml of methanol and 0.3 ml of anhydrous benzene. Ethyl propionyl acetate 12 (59.5 mg) and 1.0 *N* $NaOCH_3$ (0.07 ml) were added and the mixture was stirred at 0° under nitrogen for 2 hr and at 20° for 16 hr. The reaction mixture was neutralized with 0.1 *N* HCl and evaporated to dryness *in vacuo*. It was treated two times with toluene, dissolved in toluene, filtered, and taken to dryness under high vacuum to give 23.8 mg (90.9%) of the diketo ester 13 as an oil, ir 1735 (ester carbonyl) and 1710 cm^{-1} (keto carbonyls).

(±)-3β-*tert*-Butoxy-2,3,3a,4,5,7,8,9,9aβ,9bα-decahydro-3aβ,6-dimethyl-7-oxo-1*H*-benz[*e*]indene-8α-carboxylic Acid (15).—The crude diketo ester 13 (23.8 mg) was dissolved in 0.5 ml of tetrahydrofuran, and 0.5 ml of 0.2 *N* NaOH was added with stirring at 20° under nitrogen. The reaction mixture was allowed to stand at room temperature for 16 hr. The solvent was then evaporated *in vacuo*, and the residue was dissolved in water and extracted with chloroform to remove neutral material. The aqueous solution was carefully acidified with 2 *N* HCl and extracted with chloroform. The extract was washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated *in vacuo* to give 12.7 mg (60.8%) of the crude β-keto acid 15: uv (CH_2Cl_2) 248 nm (ε 6650); ir 1740 (carboxyl carbonyl), 1710 (saturated keto impurity), 1655 (α,β-unsaturated ketone), and 1601 cm^{-1} (conjugated double bond).

(±)-3β-*tert*-Butoxy-2,3,3a,4,5,7,8,9,9aβ,9bα-decahydro-3aβ,6-dimethyl-1*H*-benz[*e*]inden-7-one [(±)-16].—The unsaturated β-keto acid 15 (10.6 mg) was dissolved in 3 ml of toluene, and the solution was heated at reflux for 1 hr under nitrogen. The solvent was removed *in vacuo* to give 10.1 mg of crude 16 as an oil: uv 246.5 nm (ε 7340); ir 1710 (saturated keto impurity), 1655 (α,β-unsaturated ketone), and 1605 cm^{-1} (conjugated double bond). Vpc indicated 57.3% of 16 by comparison with an optically active authentic sample[9] of 16.

(±)-1β-*tert*-Butoxy-3aα,6,7,7a-tetrahydro-7aβ-methyl-4-methyleneindan-5(4*H*)-one (19).—The β-keto acid 10 (2.95 g)[3] was dissolved in a mixture of 22 ml of DMSO and 12.2 ml of 36–38% aqueous formaldehyde solution. Piperidine hydrochloride (1.35 g) was added, and the mixture was stirred under nitrogen for 3 hr. A solution of 935 mg of sodium bicarbonate in water (100 ml) was added, and the solution was extracted three times with benzene. The extract was washed with water and with saturated NaCl solution, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give 2.67 g of crude 19 as an oil, uv 227 nm (ε 4050).

A sample of 19 (236 mg) was purified by preparative thin layer chromatography on silica gel with fluorescent indicator. The sample was applied at the rate of 30 mg per plate measuring 8 in. × 8 in. × 1 mm thick. The development was carried out with a mixture of 92.5% benzene and 7.5% ethyl acetate. The area corresponding to the major component gave 153 mg (65%) of pure methylene ketone 19 as an oil which crystallized upon standing in a Dry Ice box: mp 42.5–44°; uv 231 nm (ε 4260); ir 1690 (keto carbonyl) and 1625 cm^{-1} (exocyclic conjugated double bond); nmr δ 0.78 (s, 3, 7aβ-methyl), 1.15 [s, 9, C $(CH_3)_3$], 3.60 (t, 1, C-1 proton), and 4.98 and 5.92 ppm (m, 2, C=CH_2); mass spectrum *m/e* 180 ($C_{11}H_{16}O_2$), 57 (C_4H_9).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 75.32; H, 10.25.

(±)-2,3,3a,4,5,7,8,9,9aβ,9bα-Decahydro-3β-hydroxy-3aβ,6-dimethyl-1*H*-benz[*e*]inden-7-one [(±)-7].—To the crude methylene ketone 19 (115.2 mg) was added 410 mg of freshly distilled ethyl propionyl acetate (purchased from K & K Laboratories). The mixture was cooled to 0°, and 0.87 ml of 0.1 *N* $NaOCH_3$ was added with stirring under nitrogen. The reaction mixture was allowed to stand for 18 hr at 0° and 20° for 4 hr. It was then cooled with an ice bath and neutralized with 0.87 ml of 0.1 *N* HCl. The solvent was removed *in vacuo*, and the residue was extracted with CH_2Cl_2. The extract was washed with water and a saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give 220 mg of the crude diketo ester 13 as an oil, ir 1735 (ester carbonyl) and 1710 cm^{-1} (keto carbonyls).

The compound 13 was identical with the sample obtained from the β-keto mesylate 11 as described above.

The β-diketo ester 13 (220 mg) was dissolved in 4 ml of methanol, and 4.0 ml of 2 *N* HCl was added. The reaction mixture was stirred and refluxed under nitrogen for 6 hr. It was then cooled with an ice bath, and neutalized with 0.4 ml of 19.5 *N* NaOH and then with 0.4 ml of 1.0 *N* NaOH. The solvent was evaporated *in vacuo*, and the residue was extracted two times with ethyl acetate and once with ether. The combined extract was washed once with water and two times with saturated NaCl solution. It was dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give 114 mg (100%) of crude (±)-7 as an oil that crystallized upon seeding with an authentic sample:[4a] uv 247.5 nm (ε 10,100); ir 3620 (unassociated OH), 3250–3580 (associated OH), 1728 (ester impurity), 1655 (α,β-unsaturated ketone), and 1605 cm^{-1} (conjugated double bond).

A sample of the crude BCD tricyclic compound (±)-7 (109 mg) was purified by preparative thin layer chromatography on silica gel with fluorescent indicator. The sample was applied at the rate of 27 mg per plate measuring 8 in. × 8 in. × 1 mm thick. The development was carried out with a mixture of 50% benzene–ethyl acetate. The area corresponding to the major component gave 72.5 mg (66.5%) of an oil that crystallized upon seeding with an authentic sample, uv 248 nm (ε 13,320). Trituration with a 2:1 mixture of ether–petroleum ether (bp 30–60°) gave 50.6 mg (45.4% overall yield, based on the β-keto acid 17) of pure (±)-7: mp 131–133°; uv 247.5 nm (ε 14,920); ir 3620 (unassociated OH), 3300–3550 (associated OH), 1660 (α,β-unsaturated ketone), and 1605 cm^{-1} (conjugated double bond); nmr δ 0.92 (s, 3, 3aβ-methyl), 1.80 (s, 3, C-6 methyl), 3.72 (t, 1, C-3 proton).

1-Methylsulfinyl-6-(1,3-dioxolan-2-yl)-2-heptanone (24).—To a 53% dispersion of sodium hydride in mineral oil (29.2 g), which had been washed with anhydrous hexane and dried under nitrogen, was added 378 ml of dimethyl sulfoxide (distilled from calcium hydride). The mixture was stirred under nitrogen, and it was heated slowly to 68–71°. After 1.5 hr, the evolution of hydrogen ceased, and a turbid gray solution of the sodium salt of the methylsulfinyl carbanion[17] had formed. The solution was cooled to 18°, and the ketal ester 22 (60.6 g) was added within 40 min to the stirred solution at a rate not to exceed an exothermic reaction temperature of 18–20°. It was then stirred at 25° for 1 hr. The solution was poured onto ice, neutralized with ice-cold 1 *N* HCl, and extracted with $CHCl_3$. The extract was washed with a saturated NaCl solution, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give 104 g of an oil. Volatile impurities were removed under high vacuum (bath temperature 80°) to give 52.5 g (75%) of the β-keto sulfoxide 24: uv 282 nm (ε 127); uv (0.01 *N* potassium methoxide) 252 nm (ε 5420); ir 1712 (keto carbonyl) and 1045 cm^{-1} (sulfoxide); nmr δ 1.30 (s, 3, $CH_3C<$), 1.68 (s, 4, $-CH_2CH_2-$), 2.68 [s, 5, CH_3SO- and $(-CH_2CO)_3$], 3.74 (s, 2, $-COCH_2SO-$), 3.93 (s, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{10}H_{18}O_4S$: C, 51.26; H, 7.74; S, 13.68. Found: C, 50.96; H, 7.55; S, 13.81.

6-(1,3-Dioxolan-2-yl)-2-heptanone (25). A. From the β-Keto Sulfoxide 24.—The β-keto sulfoxide 24 (40.0 g) was dissolved in a mixture of 2160 ml of tetrahydrofuran, 240 ml of H_2O, and 34 ml of 1 *N* NaOH. The solution was added at once to aluminum amalgam prepared from 46.2 g of aluminum foil, and it was shaken for 2 hr under a fast stream of nitrogen to entrain the methyl mercaptan formed. It was filtered through a pad of Celite on a sintered glass funnel; the gelatinous precipitate was washed thoroughly with ether. The filtrate was concentrated *in vacuo* to a small volume (approximately 50 ml) and extracted with ether. The extract was washed with saturated NaCl solution, dried (Na_2SO_4), treated with Norit A, filtered, and evaporated *in vacuo* to give 26.31 g (89.5%) of the ketal ketone 25 as an oil: ir 1708 cm^{-1} (keto carbonyl); nmr δ 1.32 (s, 3, $CH_3C<$), 1.65 (s, 4, $-CH_2CH_2-$), 2.13 (s, 3, CH_3CO), 2.45 (m, 2, $-CH_2CO-$) 3.93 (s, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 63.09; H, 9.42.

B. From the Ketal Acid 23.—The ketal acid 23 (348 mg)[19] was dissolved in 5 ml of anhydrous tetrahydrofuran. The solution was cooled to 0°, and 1.25 ml of a 1.6 *M* solution of methyllithium in diethyl ether was added dropwise within 1 hr, with stirring under nitrogen. The solution was allowed to come to 20°, and 2.5 ml of methyllithium reagent was added at this temperature

within 2 hr. The reaction mixture was added to crushed ice, and the organic solvents were removed *in vacuo*. The residue was extracted with ether, and the extract was washed with a saturated NaCl solution, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give 308 mg (89.5%) of crude **25**. The compound was identical by ir with a sample obtained from **24** by method A.

7-(1,3-Dioxolan-2-yl)-3-oxooctanoic Acid Ethyl Ester (20).—To a 53% dispersion of sodium hydride in mineral oil (4.55 g, 0.1 mol) which was washed with anhydrous hexane and dried under nitrogen was added 11.8 g (0.1 mol) of diethyl carbonate in 12.5 ml of anhydrous ether. This mixture was stirred under nitrogen, and 8.6 g (0.05 mol) of the ketal ketone **25** was added dropwise over a period of 2 hr. A gentle reflux was maintained throughout the addition, and refluxing was continued for an additional 1.5 hr. The mixture was then cooled with an ice bath, 20 ml of anhydrous ether and 2 ml of absolute ethyl alcohol were added, and it was stirred for 45 min to destroy any unreacted NaH. The suspension was diluted with an equal volume of ether, and the ice-cold suspension was added to a rapidly stirred cold mixture of 6 ml of glacial acetic acid and 200 ml of ice water. It was then immediately neutralized with 2 ml of a saturated $NaHCO_3$ solution. The ethereal layer was separated, and the aqueous layer was extracted two more times with ether. The extract was washed with saturated $NaHCO_3$ and saturated NaCl solutions, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give 12.1 g (99.3%) of the crude β-keto ester **20**. Fractional distillation gave 7.38 g (61.8%) of the pure β-keto ester **20**: bp 110–112° (0.02 mm); uv 244 nm (ε 1050); ir 1740 (ester carbonyl) and 1718 cm^{-1} (keto carbonyl); nmr δ 1.27 (t, 3, CH_3CH_2–), 1.30 [s, 3, $CH_3C(O)O$], 1.68 (s, 4, $-CH_2CH_2-$), 2.49 (m, 4, $-CH_2CH_2CO-$), 3.34 (s, 2, $COCH_2CO-$), 3.93 (s, 4, $-OCH_2CH_2O-$), 4.20 (q, 2, CH_3CH_2-).

Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.51; H, 8.15.

(±)-3β-*tert*-Butoxy-2,3,3a,4,5,7,8,9,9aβ,9bα-decahydro-6-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-3aβ-methyl-7-oxo-1*H*-benz[*e*]inden-8α-carboxylic Acid (27).—A mixture of 2.36 g (0.01 mmol) of freshly prepared, crude methylene ketone **19** and 2.68 g (0.011 mol) of β-keto ester **20** was cooled in an ice bath. A 0.1 *N* $NaOCH_3$ solution in methanol (20 ml) was added, and the solution was allowed to stand at 0° for 64 hr and at 20° for 4 hr. The pH of the solution was then adjusted in the cold to 7.5 with 0.5 *N* HCl and the methanol was evaporated *in vacuo*. The oily residue was dissolved in 77.5 ml of tetrahydrofuran, 77.5 ml of 0.2 *N* aqueous NaOH was added, and the mixture was stirred at 20° under nitrogen for 6 hr. The tetrahydrofuran was evaporated *in vacuo*, and the basic solution was extracted with ether. The ether extract was washed with water and saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give 1.42 g of a neutral impurity: uv 244 nm (ε 3000); ir 1710 (s) and 1670 cm^{-1} (w).

An aliquot (42.5 ml) of the aqueous basic solution (250 ml) was carefully acidified at 0° with 5.1 ml of 0.5 *N* HCl to pH 3.5. The mixture was immediately extracted with ethyl acetate and with ether. The combined extract was washed with saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give 523.8 mg (71%) of crude, unsaturated β-keto acid **27** as an amorphous solid: uv 247 nm (ε 12,550); ir 1750 (carboxyl carbonyl), 1710 (ketone impurity), 1660 and 1630 (α,β-unsaturated ketone), and 1601 cm^{-1} (conjugated double bond).

A few drops of ether were added to 742 mg of the crude solid **27**, and it was kept at −10° for 72 hr. A rather large crystalline crop was formed, which could be purified by trituration at room temperature with petroleum ether. Recrystallization from ether gave analytically pure **27**: mp 129° dec; uv 249 nm (ε 14,400); ir 1755 (carboxyl carbonyl), 1665 and 1625 (α,β-unsaturated ketone), and 1598 cm^{-1} (conjugated double bond); nmr δ 0.90 (s, 3, methyl), 1.15 [s, 9, $OC(CH_3)_3$], 1.35 [s, 3, $CH_3C(O)O$], 3.33 (q, 1, C-6 proton, $J_{6H,7eH}$ = 4.5, $J_{6H,7aH}$ = 14.5 Hz).

Anal. Calcd for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 68.84; H, 8.70.

(±)-3β-*tert*-Butoxy-1,2,3,3a,4,5,8,9,9aβ,9bα-decahydro-6-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-3aβ-methyl-7*H*-benz[*e*]inden-7-one (28).—Crude unsaturated β-keto acid **27** (523.8 mg) was dissolved in 50 ml of toluene. The solution was stirred and heated at reflux under nitrogen for 30 min. It was cooled to room temperature and extracted with a 0.5 *N* $NaHCO_3$ solution and with saturated NaCl solution. The toluene solution was dried (Na_2SO_4) and evaporated *in vacuo* to give 414.7 mg (88.1%) of unsaturated keto compound **28** as an oil: uv 247 nm (ε 10,780); ir 1665 (α,β-unsaturated keto carbonyl) and 1601 cm^{-1} (C=C).

Similar treatment of the pure β-keto acid **27** (50 mg) gave 44.9 mg of analytically pure **28**: mp 85.5–86.5° (petroleum ether); uv 248 nm (ε 16,400); ir 1663 (α,β-unsaturated keto carbonyl) and 1605 cm^{-1} (C=C).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.77; H, 10.13.

(±)-3β-*tert*-Butoxy-1,2,3,3a,4,5,5aα,6,8,9,9aβ,9bα-dodecahydro-6α-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-3aβ-methyl-7*H*-benz-[*e*]inden-7-one (29).—Crude unsaturated keto compound **28** (414.7 mg) was dissolved in 20.75 ml of absolute ethyl alcohol containing 0.5% (by volume) of triethylamine. The compound was hydrogenated in the presence of 124.5 mg of Pd on carbon catalyst at 20° and atmospheric pressure to give 407.2 mg (98%) of the saturated keto compound **29** as an oil, ir 1710 cm^{-1} (keto carbonyl).

Catalytic hydrogenation of a pure, crystalline sample of the unsaturated keto compound **28** (234 mg) under identical reaction conditions gave analytically pure **29**: mp 94.5–96° (petroleum ether); ir 1710 cm^{-1} (keto carbonyl); nmr δ 0.79 (s, 3, 3aβ-methyl), 1.13 [s, 9, $OC(CH_3)_3$], 1.33 [s, 3, $CH_3C(O)O$], 3.94 (s, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27. Found: C, 73.35; H, 10.52.

(±)-19-Nortestosterone [(±)-21].—Crude seco compound **29** (407.2 mg) was dissolved in 15 ml of methanol. To the stirred solution was added 15 ml of 2 *N* HCl, and it was heated at reflux under nitrogen for 5 hr. It was neutralized with 3 *N* NaOH and evaporated to a small volume *in vacuo*. The residue was extracted with ethyl acetate. The extract was washed with saturated NaCl solution, dried (Na_2SO_4), treated with Norit A, filtered, and evaporated *in vacuo* to give 222.7 mg of crude (±)-**21** as an amorphous solid, uv 239 nm (ε 13,710). Purification by trituration with petroleum ether and a small amount of ether gave 158.4 mg (34.2% overall yield based on the α-methylene ketone **19**) of (±)-**21**, mp 106–115°, uv 239 nm (ε 14,950). Alternatively the crude mixture may be purified by preparative tlc to give pure (±)-19-nortestosterone [(±)-**21**] in 39.7% overall yield based on **19**: mp 118–122° (lit.[26] mp 121–122°); uv nm (ε 16,500) [lit.[27] 240.5 nm (ε 17,000)]; ir 2635 (OH), 1663 (α,β-unsaturated CO), and 1620 cm^{-1} (C=C); nmr δ 0.81 (s, 3, C_{18} methyl), 3.68 (t, 1, C-17 H), 5.82 (s, 1, C-4 vinyl H). An analytical sample was prepared by trituration of the above sample with ether, mp 123–124.5°.

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 79.00; H, 9.87.

Acknowledgment.—The authors wish to express their thanks to Mr. Fred Bizzarro for his technical assistance in part of this investigation. Thanks are due to Dr. T. Williams for the nmr, to Dr. V. Toome for the uv, to Mr. S. Traiman for the ir spectroscopic data, to Dr. F. Vane for the mass spectra determinations, to Mr. H. Jenny for the vpc results, and to Dr. F. Scheidl for the microanalyses.

Registry No.—**1**, 27504-58-1; **2**, 1629-58-9; **6**, 40762-81-0; **7**, 13652-05-6; **8**, 27504-59-2; **9**, 27504-60-5; **10**, 27504-61-6; **11**, 27504-62-7; **12**, 4949-44-4; **13**, 40762-87-6; **15**, 27510-09-4; **16**, 40762-89-8; **19**, 27504-55-8; **20**, 27428-41-7; **21**, 5972-58-7; **22**, 40745-29-7; **23**, 5694-89-3; **24**, 29310-40-5; **25**, 15580-05-9; **27**, 27510-05-0; **28**, 27601-48-5; **29**, 27510-06-1; trimethyl orthoformate, 149-73-5; methanesulfonyl chloride, 124-63-0.

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The Photochemistry of Conjugated *cis*-Bicyclo[5.1.0]octenones, *cis*- and *trans*-Bicyclo[5.2.0]non-2-en-4-ones, and Their Methylene Analogs

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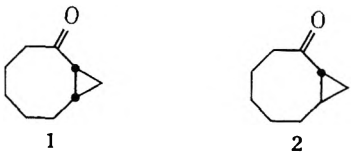
Received April 19, 1973

The photochemistry of 1,4,4-trimethyl-*cis*-bicyclo[5.1.0]oct-5-en-2-one, *cis*-bicyclo[5.1.0]oct-2-en-4-one, and their methylene derivatives has been studied. In the first instance, 1,3 shift of the bond common to the two rings occurs, with rearrangement occurring from the singlet manifold. Photoisomerization of its methylene derivative likewise is a singlet state transformation. In sharp contrast, although the 2-en-4-one bicyclic and the derived conjugated diene also undergo excited state vinylcyclopropane–cyclopentene bond reorganization, these reactions proceed readily from the respective triplet states. These differences have been rationalized in terms of conformational factors particularly as they relate to bond overlap in the S_1 or the transoid (*i.e.*, as relates to π-bond overlap) T_1 states. The *cis*- and *trans*-bicyclo[5.2.0]non-2-en-4-ones, as well as their methylene congeners, do not exhibit an analogous propensity for rearrangement. Rather, polymerization was noted in aprotic solvents throughout this latter series.

Recent comparative studies of the photochemistry of medium-ring 2-cycloalkenones and their more highly unsaturated counterparts have revealed that the additional centers of unsaturation present in the latter group of compounds, whether conjugated or not, frequently participate in chemical reaction. For example, although the propensity of *cis*-2-cycloheptenone and *cis*-2-cyclooctenone for rapid intramolecular cis–trans isomerization from their triplet states is known to be exceptionally facile,[3-5] irradiation of the cross-conjugated ketones 2,6-cycloheptadienone and 2,7-cyclooctadienone is more complicated. Under a variety of conditions there are produced intermediates, the nature of which remains to be fully clarified, which can be trapped by both protic solvents and dienes to give bicyclo[3.2.0]heptane and bicyclo[3.3.0]octane derivatives, respectively.[6,7] Also, the straightforward valence isomerization of 2,4-cycloheptadienone (as its 2,6,6-trimethyl derivative)[8] differs notably from the preference of the more flexible 2,4-cyclooctadienone homolog for conversion to its monotrans form and dimerization.[9,10] When 2,6-cyclooctadienone is irradiated in reactive solvents, trapping of the 2-trans-6-cis isomer is found, whereas inert solvents permit photorearrangement to tricyclo[3.2.1.$0^{2,6}$]octan-2-one.[9,11]

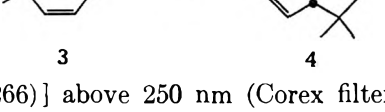
In contrast to the photochemical behavior of *cis*-2-cyclooctenone, the corresponding formally conjugated cyclopropyl analogs **1** and **2** exhibit widely differing stereochemically dependent excited-state reactivities.[12] Bicyclo[6.1.0]nonan-3-one and bicyclo[6.1.0]nonan-4-one, molecules in which the cyclopropane ring is not conjugated with the carbonyl function, also undergo facile photorearrangement.[13,14] Ostensibly, the well-recognized capability of the labile three-membered ring to transmit or extend conjugation and to exhibit many of the reactions of double bonds has encouraged the extensive investigation and delineation of excited-state cyclopropyl ketone reactivities.[15]



1 2

An intriguing question concerned the photochemical behavior of medium-ring ketones which possess a combination of both types of functional groups, *i.e.*, a double bond and a strained fused ring system. The present study had as its goals the elucidation of possible bond reorganization pathways, stereochemistry, and electronic mechanism in a series of bicyclo[5.1.0]octenones and bicyclo[5.2.0]nonenones. Because the exocyclic methylene derivatives of these ketones lack an in-plane unshared electron pair and consequently have no comparable $n \rightarrow \pi^*$ excited states from which to react, elucidation of the reactivity of the $\pi \rightarrow \pi^*$ states in these related hydrocarbons was considered to be of considerable intrinsic interest as well, and such have also been examined.[16]

1,4,4-Trimethyl-*cis*-bicyclo[5.1.0]oct-5-en-2-one (3). —Direct irradiation of **3**[17] [$\lambda_{max}^{C_2H_5OH}$ 207 nm (ϵ 3710) and 272 (266)] above 250 nm (Corex filter) in ether solution resulted in gradual transformation into a single



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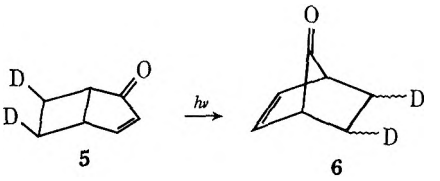
monomeric photoproduct (10% yield after 5 hr, cyclooctane as internal standard). The concurrent production of substantial quantities of polymeric material was also evident. Preparative scale gas chromatographic isolation gave an isomeric ketone identified as **4** chiefly on the basis of its spectral properties. Its infrared spectrum showed a carbonyl stretching band at 1745 cm^{-1} indicative of a five-membered ring ketone and double bond absorption at 1680 cm^{-1}. The virtually negligible electronic spectrum [$\lambda_{max}^{C_2H_5OH}$ 286 nm (ϵ 40)] attested to the absence of the original chromophore. This information, when taken together with the two-proton olefinic signal at δ 5.68 (br s), the two distinct allylic hydrogen multiplets at 2.72 (1 H, H_5) and 2.40 (2 H, H_8), the AB quartet for the α-carbonyl methylene group (2.12, J_{AB} = 16 Hz, Δ_{AB} = 19.5 Hz), and the methyl singlets at 1.29 (CH_3 group at C_1) and 1.10 (CH_3 groups at C_4), is considered to support unequivocally the structural assignment.

When the irradiation was repeated using methanol as solvent, the rate of production of **4** was significantly enhanced; this effect was not found with pentane. The photorearrangement was seen not to be completely quenchable with varying concentrations of piperylene (E_T^{trans} = 59 kcal/mol; E_T^{cis} = 57 kcal/mol) or naphthalene (E_T = 61 kcal/mol) in ether solution. Ketone **3** again polymerized slowly under these conditions. Attempts to generate the triplet of **3** by making recourse to sensitization with benzophenone (E_T = 68.8 kcal/mol) or acetone (E_T = 82 kcal/mol) under conditions where the sensitizer absorbed the major portion of the incident radiation was found to be ineffective in achieving enhanced rearrangement to **4**. Irradiations of tubes containing the sensitizers were performed competitively with direct irradiation of solutions with the identical concentrations of **3** but lacking sensitizer. After adjustment was made for the differences in light capture, sensitization was considered not to be operative.

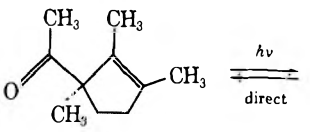
Assuming that the triplet state of **3** lies at a level capable of sensitization by one of these ketones, it can be concluded that T_1 does not rearrange. We cannot rule out the possibility that a higher triplet of **3** is responsible for the rearrangement. However, it is more likely either that the n → π^* singlet state (S_1) is involved or that an electronically excited state relaxes to a ground-state species (speculation would of course center about the C_2–C_3 trans isomer of **3**) which subsequently undergoes the intramolecular rearrangement. Although we have not distinguished between these alternatives, the behavior of the bicyclo[5.2.0]nonenones (see below) and the thermal reactivity of **3**[18] suggest that the former is the more realistic pathway.

On this basis, we are left with the first excited singlet of **3** as responsible for the observed photochemical 1,3 shift. Cargill has suggested that such processes tend to be nonconcerted reactions as evidenced by the stereorandomization of deuterium label noted in the conversion of **5** to **6**, a result inconsistent with a [$_\sigma 2_s$ + $_\pi 2_s$] pathway.[19] However, there are conflicting opinions on this point. For example, Baggiolini, Schaffner,

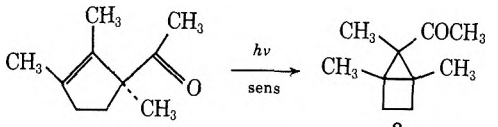


5 **6**

and Jeger[20] have observed that direct irradiation of optically active **7** proceeds intramolecularly to give racemic material of the same gross structure. Because triplet quenchers were ineffective and sensitization gave rise to the oxadi-π-methane product **8**, a concerted



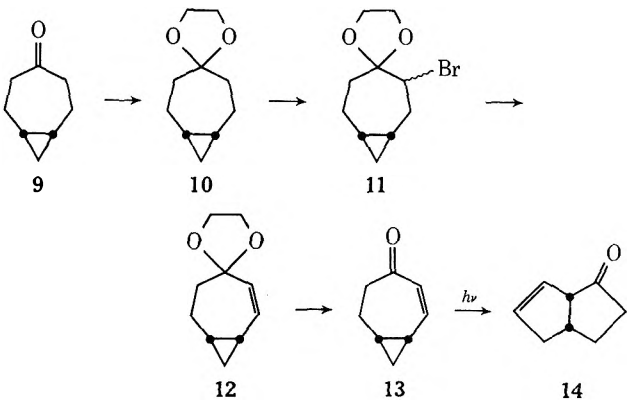
(*R*)-**7**



(*S*)-**7** **8**

reaction was considered to be operative. These apparently divergent results can be understood if electronic relaxation to ground-state diradicals operates in certain systems (*e.g.*, **5**) but not in others such as **7**. Unfortunately, because the retention of stereochemistry which accompanies the bond relocation in **3** may be the result of control by thermodynamic factors (the trans isomer of **4** would be highly strained), no definitive conclusions relating to the timing of the **3** → **4** rearrangement can be drawn at this time.

cis-**Bicyclo[5.1.0]oct-2-en-4-one** (**13**).—Treatment of ketal **10**, available in 92% yield from the known ketone **9**, with excess bromine in ether at room temperature gave monobromide **11**, which without further purification was dehydrobrominated by means of potassium *tert*-butoxide in dry dimethyl sulfoxide at room temperature (50% overall yield). Hydrolysis of the resulting monounsaturated ketal **12** with 3% sulfuric



9 **10** **11** **12** **13** **14**

acid afforded the desired **13** in 95% yield. This material exhibits an infrared carbonyl stretching frequency at 1665 cm^{-1} and an electronic spectrum (isooctane solution) characterized by maxima at 237 (ϵ 7700) and 322 nm (50) and a shoulder at 337 nm (40). Its nmr spectrum (in CCl_4) consists of a one-proton multiplet at δ 0.57, a broad absorption of area 7 at 0.9–3.05, and

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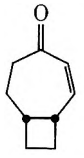
doublets (J = 12.5 Hz) at 5.83 and 6.83 due to H_3 and H_2, respectively.

The photolysis of pentane solutions of **13** through a Pyrex filter (λ >280 nm) led to the formation of a lone photoproduct in 60% yield after 1 hr. Spectral data on a purified sample of this compound revealed it to be a β,γ-unsaturated cyclopentanone (see Experimental Section). Unequivocal proof of structure **14** was achieved by direct comparison with an authentic sample of *cis*-bicyclo[3.3.0]oct-7-en-2-one.[21]

In apparent contrast to **3**, the photorearrangement of **13** in acetone solvent provided a yield of **14** (82% after 1 hr) greater than that realized in the direct irradiation. Although these observations might be considered superficial since the acetone runs generated measurably less polymer than the pentane experiments, sensitization is operative since the rate of conversion to **14** remains unabated despite absorption by acetone of greater than 90% of the incident radiation. Finally, although benzophenone was expectedly ineffective as a sensitizer, the isomerization was not quenched by concentrations of naphthalene and piperylene as high as 1 M.

These results support the conclusions that under the conditions of direct irradiation either n $\rightarrow$ π^* singlet states are primarily involved or rates of intramolecular rearrangement of the corresponding triplet states are faster than diffusion control. Whatever the case, the formation of the same product from the preformed triplet reveals that rearrangement by the respective triplet state is possible in this instance. That the singlet state of **13** can undergo cyclopropyl bond cleavage and allylic rearrangement is suggested by the thermal behavior of this ketone.[18]

cis- and *trans*-**Bicyclo[5.2.0]non-2-en-4-ones (15 and 16).**[22]—This aspect of the work was concerned with the behavior of the structurally less constrained epimeric bicyclo[5.2.0]nonenyl ketones **15** and **16**. Although



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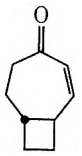

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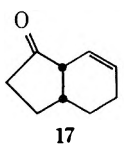
these systems no longer have the latent potential for vinylcyclopropane rearrangement, which generally is thermodynamically exothermic by about 25 kcal/mol,[23] they are free to undergo an analogous vinylcyclobutane bond reorganization. Moreover, relatively ready accessibility[22] to both the cis and trans isomers in this series promised potential solution to the question of whether concerted 1,3 carbon shifts or stepwise pathways were operative. The ground-state energy difference between **17** and **18** did not appear to be sufficiently great to deter their direct formation from **15** and **16**, respectively, should synchronous processes be operational. On the other hand, the difference was deemed adequate to guarantee the favored production of **17** should dipolar or diradical intermediates intervene.



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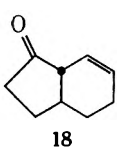

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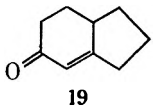
It was soon discovered, however, that these *a priori* considerations were not to apply because **15** and **16** do not follow the photochemical precedent established by **13**. Thus, upon photolysis (200-W Hanovia lamp) of **15** in dilute pentane solution through Pyrex, rapid disappearance of starting material was observed ($t_{1/2}$ ~30 min) but no new volatile products were generated. After 1 hr, little **15** remained (cyclododecane as internal standard) and a white, insoluble material had deposited on the walls of the vessel. Similar results were realized in dilute acetone solution, in which case complete reaction was noted after only 30 min.

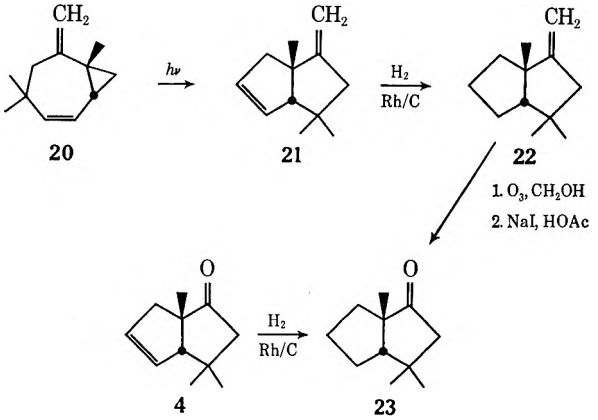
Comparable photolysis of **16** in acetone, glyme, or pentane solution likewise resulted only in rapid conversion to polymeric substances. No monomeric products in significant quantity (>1%) were detected. In contrast, when methanol was employed as solvent, a mixture of five major components was formed. Four of these substances were identified as methoxy ketones and were not further characterized. The fifth component, amounting to 9% of the mixture, was identified as **19** by comparison with an authentic sample.[24] Since



19

this conjugated ketone was a minor product, mechanistic considerations of its origin were not given further attention.

2-Methylene-1,4,4-trimethyl-*cis*-bicyclo[5.1.0]oct-5-ene (20).—The divinylcyclopropane **20** was conveniently prepared by the Wittig reaction of **3** with methylenetriphenylphosphorane. This colorless liquid exhibited only intense end absorption (C_2H_5OH solution) in the ultraviolet region. Upon direct irradiation of **20** in pentane or methanol through Vycor (λ >220 nm), an isomeric hydrocarbon was produced in 24 and 56% yields, respectively, after 10 hr. There was also formed 1–3% of an unidentified volatile substance. The primary photoproduct showed nmr features entirely compatible with structure **21**. Corroborative evidence for this assignment was gained ultimately by selective hydrogenation to **22** over 5% rhodium on carbon and



(21) N. A. Lebel and L. A. Spurlock, *Tetrahedron*, **20**, 215 (1964). We thank Professor Lebel for generously providing us with a sample of **14**.

(22) Discussion of the synthesis of these compounds is deferred to the accompanying paper.

(23) W. von E. Doering and E. K. G. Schmidt, *Tetrahedron*, **27**, 2005 (1971), and relevant references cited therein.

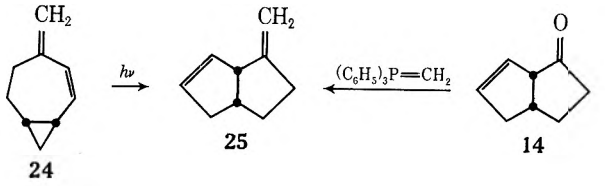
(24) G. S. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

ozonolysis of this dihydro derivative to the cyclopentanone derivative **23**. This compound was identical with that obtained from independent hydrogenation of **4**. The attempted conversion of **4** to **21** under Wittig conditions was not successful, perhaps because of steric factors.

In additional studies, it was observed that photolysis of **20** in dilute acetone solution through either Vycor or Pyrex afforded only minute amounts of **21**. However, extensive polymerization was noted. A similar result was obtained when we sought to generate the triplet of **20** by benzophenone sensitization (*tert*-butyl alcohol solution) under conditions where this ketone absorbed over 97% of the incident light. The efficiency of the triplet transfer to **20** was unequivocally established in the latter series of experiments by its effective quenching of benzopinacol formation when benzhydrol was added. Since **21** was independently found to be stable to these conditions, the polymerization cannot be construed as arising from the excited triplet state of **21**.

Accordingly, there exists a marked reluctance of the **20** triplet to rearrange to **21**. Since intersystem crossing of $S_1 \rightarrow T_1$ is not generally observed in olefinic systems, it appears that, in the case of **20**, S_1 leads to rearrangement but the triplet is ineffective in this regard and engenders only polymerization. This gross behavior parallels the photochemistry of structurally related ketone **3**, despite the fact that different excited states are quite likely involved (n $\rightarrow \pi^*$ for **3** and $\pi \rightarrow \pi^*$ for **20**).

4-Methylene-*cis*-bicyclo[5.1.0]oct-2-ene (24).—The synthesis of **24** required only a Wittig reaction on ketone **13**. The electronic spectrum of this diene (isooctane) consisted of a lone maximum at 237 nm (ϵ 17,030). Sensitized photolysis of **24** in dilute acetone solution (Pyrex optics) resulted in rapid conversion in high (95+%) yield to a single photoproduct. The resulting colorless oil was readily identified as **25** by virtue of its spectral characteristics and unequivocal synthesis from **14**. When pentane was employed as

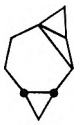


24 25 14

solvent (Vycor filter), the process became more complex; bicyclic diene **25** was again formed as the major product (53% yield), but four additional minor components (not characterized) were also observed. A separate experiment clearly showed that these lesser products were not derived from **25** since, except for a small amount of polymer formation, the latter methylene derivative was stable to the irradiation conditions. Since the triplet-sensitized process afforded only **25** and no side products, the occurrence of singlet transfer to **24** in acetone solution is highly remote.

Consequently, the reactivity profile of **24** lies in marked contrast to the photochemical behavior displayed by **20**, two conjugated methylenecyclohexenes,[25] and a 1-methylene-2,5-cyclohexadiene derivative.[26] In these latter examples, there is seen a complete absence of monomeric products in the sensitized experiments, the di-π-methane rearrangements occurring preferentially from the respective singlet excited states. Owing to observations of efficient triplet bond reorganization in certain rigid bicyclic polyene hydrocarbons lacking exocyclic methylene groups, the absence of triplet rearrangement in molecules such as **31** was attributed to a "free rotor" effect.[27] According to this concept, triplet energy was capable of efficient dissipation as a result of free rotation about bonds of low π order, particularly that to the exocyclic carbon atom. However, Kende's recent finding that 2-methylene-6,7-benzobicyclo[3.2.2]nona-3,6,8-triene, a "free rotor" polyene, exhibits highly regiospecific rearrangement, preferentially *via* a triplet excited state,[28] points to limitations of the "free rotor" hypothesis.[27c]

A possible alternative explanation for the differing behavior of **20** and **24** may be that the energy of the triplet $\pi \rightarrow \pi^*$ excitation of **24** is heavily concentrated in the conjugated diene moiety, a phenomenon which is expected to facilitate migration of the stereoelectronically favored internal cyclopropyl bond. Reaction products which are to be expected[29] from bicyclobutane intermediate **26** were carefully sought but could



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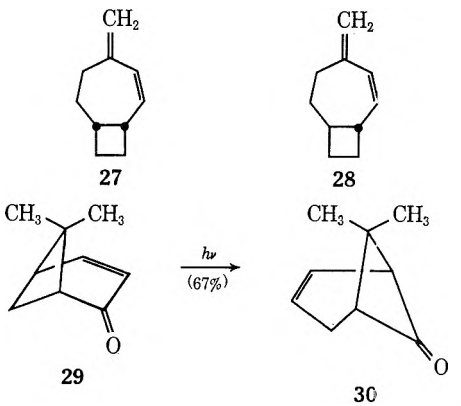
not be found when **24** was irradiated in methanol. Under these conditions, no solvent-incorporated products were found and the results were approximately the same as those realized in pentane solution. Therefore, the cyclopropyl function appears to exert a significant influence on the reactivity of the transoid diene moiety in the excited states of **24**.

***cis*- and *trans*-4-Methylenebicyclo[5.2.0]non-2-enes (27 and 28).**—In an effort to derive added significance from the highly stereoselective conversion of **24** to **25**, our study was expanded to include the photochemistry of dienes **27** and **28**. Photochemical shifts of a cyclo-



27 28 29 30

(25) (a) H. E. Zimmerman and G. E. Samuelson, *J. Amer. Chem. Soc.*, **89**, 5971 (1967); (b) W. G. Dauben and W. A. Spitzer, *ibid.*, **90**, 802 (1968).

(26) H. E. Zimmerman, P. Hackett, D. F. Juers, and B. Schröder, *J. Amer. Chem. Soc.*, **89**, 5973 (1967).

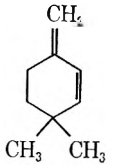
(27) (a) J. S. Swenton, A. R. Crumrine, and T. J. Walker, *J. Amer. Chem. Soc.*, **92**, 1406 (1970); (b) H. E. Zimmerman and G. R. Epling, *ibid.*, **92**, 1411 (1970); (c) *ibid.*, **94**, 8749 (1972).

(28) Z. Goldschmidt and A. S. Kende, *Tetrahedron Lett.*, 4625 (1971).

(29) W. G. Dauben and C. D. Poulter, *Tetrahedron Lett.*, 3021 (1967); W. G. Dauben and J. S. Ritscher, *J. Amer. Chem. Soc.*, **92**, 2925 (1970).

butane bond are rare, but nevertheless known, as exemplified by the conversion of verbenone (**29**) to chrysanthenone (**30**).[30] Comparable migrations in purely olefinic systems have, however, not been reported.

Upon direct irradiation in pentane through Pyrex, both **27** and **28** were found to be slowly consumed with concomitant generation of polymeric substances. Sensitized irradiation in acetone solution gave comparable results. This behavior is exceedingly reminiscent of the case of **31**.[25b] In this example, sensitized photolysis in pentane and methanol as well as direct irradiation in pentane gave only higher molecular weight products. Only when irradiated directly in methanol did **31** form monomeric products. These were identified as methyl ethers derived from solvent capture of intermediate bicyclobutane **32**.



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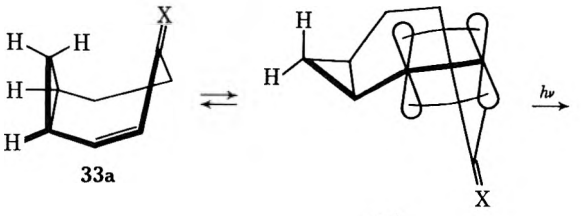
When **27** and **28** were photolyzed directly in methanol, slow disappearance of the dienes was again observed. However, volatile products were not in evidence. Thus we conclude tentatively that these dienes probably do not experience comparable electronic reorganization to give bicyclobutane derivatives.

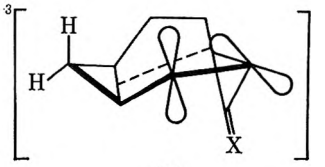
Discussion

A most striking aspect of the photochemistry of the *cis*-bicyclo[5.1.0]octenones and their methylene derivatives is the dramatic difference in behavior of the "cross-functionalized" (**3** and **20**) and linearly conjugated systems **13** and **24**. Although relocation of the strained internal bond operates in all four examples, the vinylcyclopropane rearrangements occur uniquely by way of the singlet excited states of **3** ($n \rightarrow \pi^*$) and **20** ($\pi \rightarrow \pi^*$). In contrast, the isomerizations of **13** and **24** are efficient from their triplet manifolds. That bicyclic product (*i.e.*, **14**) was also found in the direct irradiation of **13** leaves unproven whether this ketone is formed from the singlet state as well. The presence of a cyclopropane ring is essential to photorearrangement of **13** and **24**, since the homologous cyclobutane derivatives **15**, **16**, **27**, and **28** do not give any evidence of isomerization.

Examination of Dreiding models of **13** and **24** has indicated the two more stable ground-state conformations of these molecules to be as shown in **33** with **33b** enjoying fewer nonbonded interactions. In neither structure is the C_2–C_3 π bond seen to be aligned stereoelectronically for favorable overlap with the strained C–C bond common to the two rings. The difference in behavior of the singlet and triplet states of **33** may arise not only as a consequence of spin pairedness but perhaps as importantly because of geometry and energy dissipation considerations. Thus, when the energies of ethylene electronic states *vs.* angle of twist as calculated by several methods[31] are considered, crossing of ground state (S_0) and T_1 potential energy surfaces, but not that of the first excited singlet state (S_1), is indicated. This fact, coupled with the favored transoid nature of triplets (see, for example, **34**), suggests the



33a **33b**



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possibility of allowed adiabetic conversion of the T_1 states of the linear conjugated molecules to the [3.3.0] bicyclic products. Hence, intersystem crossing in ketone **13** may well be facilitated because crossing from its triplet state potential energy surface to product ground state may be of high efficiency.

When inquiry is made into the conformational features of **3** and **20**, Dreiding models provide evidence for the increased flexibility of these bicyclics relative to **33**. Quite suitable overlap of the exocyclic π network with the internal cyclopropane bond is attainable with little dihedral angle torsion of the relevant orbitals. As a direct consequence of the continuous interaction realizable with this ever lengthening σ bond, the singlet excited states of **3** and **20** proceed with significant usage of this mechanism. The facility of internal bond fission which operates in these examples seemingly precludes intersystem crossing of the singlet $n \rightarrow \pi^*$ state of **3** to the triplet manifold.

Although other investigators have emphasized models in which ground-state geometry serves as a stereochemical determinant,[32] it is also entirely possible that these same characteristics dictate from which of the excited state manifolds bond relocation can occur most readily. In this regard, it is interesting that the fused cyclobutane derivatives **15**, **16**, **27**, and **28** do not partake of similar reactions. This absence of an inducement for rearrangement, which likely has its origins in the obvious diminution of ring strain, supports the proposition that a composite of factors determines the suitability of a molecule for excited state transformation.

Experimental Section

Melting points are corrected. Proton magnetic resonance spectra were obtained with a Varian A-60A spectrometer and apparent coupling constants are cited. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All photolyses were conducted in the absence of oxygen and continuous introduction of O_2-free nitrogen was accomplished where possible.

(30) (a) J. J. Hurst and G. H. Whitham, *J. Chem. Soc.*, 2864 (1960); (b) W. F. Erman, *J. Amer. Chem. Soc.*, **89**, 3828 (1967).

(31) R. S. Mulliken and C. C. J. Roothan, *Chem. Rev.*, **41**, 219 (1947); U. Kaldor and I. Shavitt, *J. Chem. Phys.*, **48**, 191 (1968); N. C. Baird and R. M. West, *J. Amer. Chem. Soc.*, **93**, 4427 (1971).

(32) W. G. Dauben, *Chem. Weekbl.*, **60**, 381 (1964); J. P. Malrieu, *Photochem. Photobiol.*, **5**, 291, 301 (1966); J. E. Baldwin and S. M. Krueger, *J. Amer. Chem. Soc.*, **91**, 6444 (1969).

Irradiation of 1,4,4-Trimethylbicyclo[5.1.0]oct-5-en-2-one (3).—A solution of 2.0 g of 3[17] in 450 ml of reagent-grade acetone was irradiated with a 450-W Hanovia mercury vapor lamp in a standard quartz immersion well fitted with a Corex filter. The progress of the reaction was followed by withdrawal of small aliquots at periodic intervals and analyses of these by vpc methods.[33] After 5 hr, the solvent was carefully evaporated and the nonpolymeric residue (1.9 g) was submitted to preparative vpc purification.[33] The lone photoproduct, isolated as a colorless liquid in 10% yield, was identified as 4: ν_{max}^{neat} 1745 and 1680 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 286 nm (ϵ 40); $\delta_{TMS}^{CDCl_3}$ 1.10 (s, 6, methyls), 1.29 (s, 3, methyl at C_1), 2.12 (AB pattern, J_{AB} = 16 Hz, Δ_{AB} = 19.5 Hz, $-CH_2CO-$), 2.40 (m, 2, H_8), 2.72 (m, 1, H_5), and 5.68 (br s, 2, olefinic). The semicarbazone derivative melted at 202–204°.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.50; H, 9.84.

For quantitative work, accurately weighed amounts of **3** and cyclooctane were dissolved in 3 ml of the solvent of choice and placed in quartz test tubes which were affixed in vertical array around the immersion well. Each tube was then tightly stoppered with a serum cap which permitted the withdrawal of aliquots with a microsyringe for vpc analysis. Percentage compositions (Table I) were calculated according to established procedures.[34]

TABLE I

PERCENTAGE COMPOSITION RATIOS FOR THE IRRADIATION OF 3 UNDER VARIOUS CONDITIONS

Solvent (filter)	Time, hr	Composition, %[a] 3	4	Solvent (filter)	Time, hr	Composition, %[a] 3	4
Methanol	1	33	5	Pentane	1	31	Trace
(Vycor)	2	13	10	(Vycor)	2	9	Trace
	3	8	8				
Ether	1	61	8	Acetone	1	87	4
(Corex)	2	53	10	(Corex)	2	74	7
	3	35	8		3	70	9
	4	31	8		4	61	9
	5	27	8		5	58	10
Naphthalene	28	15	2	Piperylene	37	10	3
(0.1 *M*) in				(0.1 *M*) in			
ether	32	13	Trace	ether	40	10	3
(Corex)				(Corex)			
	49	7	Trace		53	9	2
	70	5	Trace		68	10	
	100				100		

[a] Cyclooctane was used as the internal standard.

***cis*-Bicyclo[5.1.0]octan-4-one Ethylene Ketal (10).**—A mixture of 4.00 g (32.2 mmol) of 9,[35] 2.20 g (34.5 mmol) of ethylene glycol, and 60 mg of *p*-toluenesulfonic acid monohydrate in 250 ml of benzene was heated under reflux for 12 hr with azeotropic removal of water. The benzene solution was washed with saturated aqueous sodium bicarbonate (2 × 50 ml), water (2 × 50 ml), and saturated sodium chloride (1 × 50 ml) and dried, and the solvent was removed *in vacuo*. The residual oil was distilled to give 4.98 g (92%) of 10: bp 62–64° (1.0 mm); $\delta_{TMS}^{CDCl_3}$ 3.79 (s, 4, $-CH_2O-$), 0.3–2.3 (br m, 11), and −0.06 (m, 1, H_8).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.66; H, 9.63.

***cis*-Bicyclo[5.1.0]oct-2-en-4-one Ethylene Ketal (12). A. Bromination of 10.**—Bromine was added dropwise to a stirred solution of 2.85 g (17.0 mmol) of 10 in 100 ml of anhydrous ether at such a rate as to maintain the bromine coloration. After 3.73 g (23.3 mmol) of bromine had been added the uptake ceased. Twenty milliliters of a solution of monosodium ethyleneglycolate [from 880 mg (38 mg-atoms) of sodium in 20 ml of ethylene glycol] was added and the two-phase system was stirred for 5 min at room temperature. The reaction mixture was poured into 100 ml of water, the ether layer was separated, and the aqueous phase was extracted with a further 150 ml of ether. The combined ether extracts were washed with water and saturated sodium chloride, dried, and evaporated *in vacuo* to give 4.14 g of the crude bromination product 11 as a viscous yellow oil.

B. Dehydrobromination of 11.—To a solution of the above material in 60 ml of anhydrous dimethyl sulfoxide was added 4.30 g (38.4 mmol) of potassium *tert*-butoxide. After the initial exothermic reaction had subsided, the dark red solution was stirred at room temperature for 1.5 hr, poured into saturated sodium chloride solution (120 ml), and extracted with pentane (4 × 130 ml). The combined pentane layers were washed with water (2 × 100 ml) and saturated aqueous sodium chloride (1 × 100 ml), dried, and evaporated *in vacuo* to give 2.10 g of a yellow oil consisting of two components in a ratio of 86:14.[36] Preparative vpc separation of this mixture at 120° afforded 1.35 g (48% from 10) of 12: $\delta_{TMS}^{CCl_4}$ 5.75 (d with additional splitting, J = 12 Hz, 1, olefinic), 5.16 (d, J = 12 Hz, 1, olefinic), 3.83 (s, 4, $-CH_2O-$), 0.6–2.6 (br m, 7), and 0.19 (m, 1, H_8). The analytical sample was prepared by molecular distillation [55° (1 mm)].

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.05; H, 8.45.

The minor component (14%) was subsequently identified as the corresponding ketone (13).

***cis*-Bicyclo[5.2.0]oct-2-en-4-one (13).**—A mixture of 1.44 g (8.7 mmol) of 12 and 3.5 ml of 3% sulfuric acid was shaken at room temperature for 15 min. Water (15 ml) was added and the product was extracted with ether (2 × 50 ml). The ethereal solution was washed with saturated aqueous sodium bicarbonate (1 × 20 ml) and sodium chloride solutions (1 × 20 ml), dried, and evaporated *in vacuo* at 0° to give 1.02 g (95%) of colorless oil which was homogeneous by vpc. Distillation afforded 845 mg (78.5%) of pure 13: bp 55–57° (1.2 mm); $\nu_{max}^{CCl_4}$ 1665 cm^{-1}; $\lambda_{max}^{isooctane}$ 237 nm (ϵ 7700), 322 (50), and 337 (sh, 40); $\delta_{TMS}^{CCl_4}$ 6.83 (d with additional coupling, J = 12.5 Hz, 1, olefinic), 5.83 (d, J = 12.5 Hz, 1, olefinic), 0.9–3.05 (br m, 7), and 0.57 (m, 1, H_8).

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.60; H, 8.27.

Photorearrangement of 13.—A solution of 300 mg of 13 in 20 ml of pentane was irradiated for 2.5 hr under nitrogen in a quartz test tube attached to a quartz immersion well fitted with a 200-W Hanovia mercury arc and Pyrex filter. Removal of the solvent *in vacuo* at 0° gave 250 mg of a yellow oil. The photoproduct (116 mg, 39%) was isolated by preparative vpc at 90°: $\nu_{max}^{CCl_4}$ 1742 cm^{-1}; $\lambda_{max}^{isooctane}$ 284 nm (sh, ϵ 45), 293 (60), 302.5 (70), 312.5 (60), and 323 (sh, 30); $\delta_{TMS}^{CCl_4}$ 5.58 (symmetrical 14-line m, 2, olefinic) and 1.2–3.45 (br, 8 H). This ketone was identical in all respects with an authentic sample of 14.[21]

The semicarbazone of 14 was prepared in the usual manner and after recrystallization from aqueous ethanol showed mp 165.5–166.5° (lit.[21] mp 166.5–167.2°).

Analytical studies were conducted with accurately weighed mixtures of *ca.* 30 mg of 13 and *ca.* 10 mg of cyclooctane in 3 ml of purified pentane. Product composition data (Table II) were obtained as before and the photolyses were conducted as described above (Pyrex filter).

2-Methylene-1,4,4-trimethyl-*cis*-bicyclo[5.1.0]oct-5-ene (20).—To a suspension of 3.6 g (0.011 mol) of methyltriphenylphosphonium bromide in 50 ml of anhydrous ether under nitrogen was added dropwise 4.3 ml (0.011 mol) of 1.6 *M* *n*-butyllithium in hexane. After this mixture was stirred for 3 hr, a solution of 1.64 g (0.01 mol) of 3 in 10 ml of anhydrous ether was added dropwise and the resulting suspension was refluxed for 12 hr. Water (75 ml) was added, the ether layer was separated, and the aqueous layer was extracted with ether. The combined ethereal layers were washed with brine, dried, and carefully concentrated. The oily residue was taken up in pentane and the insoluble solids were separated by filtration. The filtrate was carefully concentrated and distilled to afford 0.8 g (50%) of 20: bp 72–75° (1 mm); $n^{24}D$ 1.4887; $\lambda_{max}^{C_2H_5OH}$ 275 nm (ϵ 140); $\delta_{TMS}^{CDCl_3}$ 5.20 (m, 4, vinyl), 2.17 (m, 2, allylic), 1.20, 0.95, 0.83 (s, 3 each, methyls), and 0.9 (m, 3, cyclopropyl).

Anal. Calcd for $C_{12}H_{18}$: C, 88.82; H, 11.19. Found: C, 88.90; H, 11.18.

Irradiation of 20.—A solution of 2.0 g of 20 in 450 ml of anhydrous methanol was irradiated with a 450-W mercury arc placed in a quartz immersion well fitted with a Vycor filter. Progress of the reaction was followed by withdrawal of small aliquots at periodic intervals. After 10 hr, the solution was carefully concentrated and the residual oil was subjected to

(33) A 6 ft × 0.25 in. aluminum column packed with 5% SF-96 on 60–80 mesh Chromosorb G was employed.

(34) L. A. Paquette and O. Cox, *J. Amer. Chem. Soc.*, **89**, 5633 (1967).

(35) A. C. Cope, S. Moon, and C. H. Park, *J. Amer. Chem. Soc.*, **84**, 4843 (1962).

(36) This vpc analysis was performed with the aid of a 5.5 ft × 0.25 in. aluminum column packed with 20% SE-30 on 60–80 mesh Chromosorb W.

TABLE II

PERCENTAGE COMPOSITION RATIOS FOR THE IRRADIATION OF 13 UNDER VARIOUS CONDITIONS

Solvent	Time, min	Composition, %[a] 13	14	Solvent	Time, min	Composition, %[a] 13	14
Pentane	15	55	27	Acetone	15	66	29
	30	29	48		30	43	52
	45	12	57		45	23	73
	60	4	61		60	13	82
	75	<2	63		75	8	88
Ether (0.67 *M* in benzophenone)	20	51	15	Ether (1.0 *M* in naphthalene)	20	*b*	21
	30	37	19		30	*b*	33
	60	28	33		60	*b*	50
	75	23	37		75	*b*	60
	105	14	47				
	135	9	50	Ether (1.0 *M*)	20	32	29
					30	25	38
					60	6	50
					75	4	54

[a] Cyclooctane was utilized as the internal standard. [b] The concentration of **13** could not be determined in these runs owing to overlapping with the naphthalene peak.

preparative vpc isolation.[37] The lone product formed in 56% yield was identified as **21**: $\delta_{TMS}^{CDCl_3}$ 5.67 (m, 2, vinyl), 4.77 (m, 2, exo methylene), 2.84 (m, 3), 2.1 (m, 1), 1.27 0.99, and 0.91 (s, 3 each, methyls).

Anal. Calcd for $C_{12}H_{18}$: C, 88.82; H, 11.19. Found: C, 88.96; H, 11.29.

For the quantitative work in Table III, carefully weighed amounts of **20** and cyclooctane were dissolved in 3 ml of the solvent of choice and placed in quartz test tubes which were affixed in vertical array around the immersion well. Each tube was tightly stoppered with a serum cap and the photolyses were conducted as predescribed (Vycor filter).

TABLE III

PERCENTAGE COMPOSITION RATIOS FOR THE IRRADIATION OF 20 UNDER VARIOUS CONDITIONS

Solvent	Time, hr	Composition, %[a] 20	21	Solvent	Time, hr	Composition, %[a] 20	21
Acetone	2	47	4.5	Pentane	2	85	12
	4	21	5		4	70	20
	6	6	3		6	60	25
	8	3	3		8	43	24
Methanol	2	75	19	Acetone (Pyrex)	2	82	1
	4	41	35		4	60	2
	6	31	44		6	41	3
	8	14	47		8	33	2
	10	3	56				

[a] Cyclooctane served as the internal standard.

(37) A 6 ft × 0.25 in. aluminum column packed with 5% Carbowax on 60–80 mesh Chromosorb G was utilized for this separation.

Hydrogenation of 4.—A solution of 100 mg of **4** in 20 ml of ether containing 30 mg of 5% rhodium on carbon was hydrogenated at 25° and atmospheric pressure. After 20 min, approximately 1 equiv of hydrogen was taken up. The reaction mixture was filtered, carefully concentrated, and subjected to preparative vpc purification[37] to give **23** as a colorless liquid: $\delta_{TMS}^{CCl_4}$ 0.85–2.5 (9 H), 1.18, 1.07, and 1.05 (s, 3 each, methyls); $\nu_{max}^{CCl_4}$ 1735 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.52; H, 10.94.

Hydrogenation of 21.—A solution of 200 mg of **21** in 30 ml of pentane containing 50 mg of 5% rhodium on carbon was hydrogenated as above for 1 hr, the time required for slightly more than 1 molar equiv of hydrogen to be consumed. Preparative vpc purification[37] afforded 80 mg (40%) of **22**, which showed evidence of an exocyclic methylene group at δ 4.75 (2 H) in its nmr spectrum ($CDCl_3$).

Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.48; H, 12.68.

Ozonolysis of 2.—A solution of 150 mg of **22** in 10 ml of methanol cooled to −78° was treated with ozone until the solution was saturated (bluish tint). A solution of 500 mg of sodium iodide and 0.2 ml of acetic acid in 1 ml of methanol diluted with 10 ml of water was added and solid sodium bisulfite was introduced to destroy the resulting iodine. The product was extracted with ether and isolated by preparative vpc.[37] Its infrared and nmr spectra were superimposable with those of **23** isolated above.

4-Methylene-*cis*-bicyclo[5.1.0]oct-2-ene (24).—Reaction of 610 mg (5.0 mmol) of **13** with 2.68 g (7.5 mmol) of methyltriphenylphosphonium bromide and 7.5 mmol of *n*-butyllithium in hexane dissolved in 50 ml of anhydrous ether was carried out in the predescribed fashion. Distillation of the residue *in vacuo* gave 310 mg (52%) of **24**: bp 68–70° (20 mm); $\lambda_{max}^{isooctane}$ 237 nm (ϵ 17,000); $\delta_{TMS}^{CCl_4}$ 5.88 (s, 2), 4.84 (s, 2), 0.6–2.7 (br, 7), and 0.22 (m, 1).

Anal. Calcd for C_9H_{12}: C, 89.94; H, 10.06. Found: C, 89.66; H, 9.87.

Photorearrangement of 24.—A solution of 200 mg of **24** in 20 ml of acetone was irradiated for 3.25 hr as previously described using a 450-W Hanovia lamp and Pyrex optics. The majority of the solvent was removed by distillation at atmospheric pressure through a small Vigreux column. The residue was submitted to preparative vpc isolation.[38] There was obtained 81 mg (40%) of **25**: $\delta_{TMS}^{CCl_4}$ 5.49 (s, 3), 4.79 (septet, 2), 3.5 (br d, 1) and 1.0–3.0 (br, 7). The analytical sample was prepared by molecular distillation at 50–55° (35 mm).

Anal. Calcd for C_9H_{12}: C, 89.94; H, 10.06. Found: C, 89.86; H, 10.06.

2-Methylene-*cis*-bicyclo[3.3.0]oct-7-ene (25).—Treatment of 100 mg (0.82 mmol) of **14** with 1.64 mmol of methylenetriphenylphosphorane in anhydrous ether as previously outlined afforded, after preparative vpc isolation[38] at 70°, 27 mg (27%) of **25** identical in all respects with the sample isolated above.

Acknowledgment.—Partial financial support of this research has been provided by the Army Research Office (Durham).

Registry No.—**3**, 24217-77-4; **4**, 40905-63-3; **4** semicarbazone, 40905-64-4; **9**, 40905-65-5; **10**, 24217-78-5; **11**, 40905-67-7; **12**, 24217-79-6; **13**, 24217-80-9; **14**, 10095-78-0; **20**, 24217-81-0; **21**, 40905-72-4; **22**, 40905-73-5; **23**, 40905-74-6; **24**, 24217-82-1; **25**, 24217-83-2; ethylene glycol, 107-21-1.

(38) A 5.5 ft × 0.25 in. aluminum column packed with 10% SF-96 on 60–80 mesh Chromosorb G was employed.

Thermochemical Behavior of Conjugated *cis*-Bicyclo[5.1.0]octenones, *cis*- and *trans*-Bicyclo[5.2.0]non-2-en-4-ones, and Their Methylene Analogs

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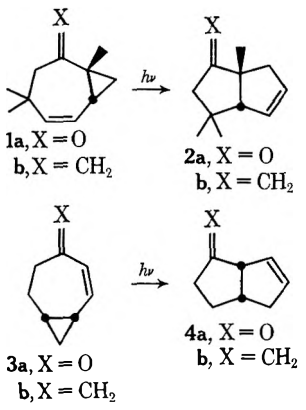
Received April 19, 1973

The pyrolysis of *cis*-bicyclo[5.1.0]oct-2-en-4-one (**3a**), *cis*-bicyclo[5.1.0]oct-5-en-2-one (**1a**), *cis*-bicyclo[6.1.0]-non-6-en-2-one (**25**), and their methylene derivatives has been studied in a flow system in the 300–600° range. Three major processes obtain, namely, 1,5-homodienyl hydrogen shift, ring contraction by 1,3 shift of the internal cyclopropane bond, and isomerization to a less strained bicyclic system by vinylcyclopropane rearrangement involving an external cyclopropyl bond. However, not all three structural types give evidence of totally similar chemical behavior and these differences are discussed. Thermal activation of *cis*- and *trans*-bicyclo[5.2.0]-non-2-en-4-one and their methylene analogs exhibit, in contrast, a major tendency for fragmentation with loss of ethylene. Bond relocation to afford [3.2.2] bicyclic products does operate in certain examples, but a stereochemical dependence is noted. Most interestingly, no 1,3 shift of the central cyclobutane bond was evidenced in any of the cases studied. This and other marked divergences in behavior between the vinylcyclopropane and vinylcyclobutane systems are presented in a mechanistic framework.

cis-Bicyclo[5.1.0]oct-5-ene derivatives **1** have been discovered to transmute to **2** upon irradiation, with vinylcyclopropane rearrangement occurring from the respective singlet states.[2] A formally analogous skeletal change takes place during photoexcitation of **3**, but the comparison is superficial since **3a** and **3b** preferably



rearrange from their T_1 excited states.[2] Attempts to photoisomerize *cis*- and *trans*-bicyclo[5.2.0]non-2-en-4-one and their methylene derivatives have to date afforded polymeric materials, except in protic media where solvent incorporation occurs in some instances.[2] In connection with these photochemical studies on medium ring ketones and olefins possessing a double bond and a cyclopropane or cyclobutane ring in conjugation, we have examined the thermally induced transformations of such substrates for comparison purposes. Since vibrationally excited molecules rearrange, in general, *via* singlet biradical intermediates if concerted pathways are unavailable, it was the purpose of this investigation to determine the consequence of thermal activation on vinylcyclopropane and vinylcyclobutane systems incorporated into various medium ring frameworks.

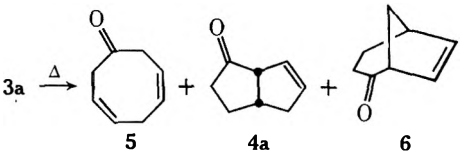
***cis*-Bicyclo[5.1.0]oct-2-enes 3a and 3b.**—Pyrolysis of **3a** in a flow system for short contact times ($\leq$3 sec) at reduced pressure and moderate temperatures (312–430°) resulted in rather efficient conversion to 3,6-cyclooctadienone (**5**, Table I). At more elevated temperatures, the quantities of **3a** and **5** in the pyrolysate

TABLE I

PYROLYSIS OF **3a** AT VARIOUS TEMPERATURES

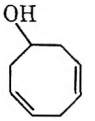
	Pyrolysate composition, %				
Temp, °C	**3a**	**5**	**4a**	**6**	Unknowns
312	78	22			
350	53	47			
390	10	89			1
432	10	85			5
470	5	71	8	11	5
530	12	42	18	21	7
600			51	24	25

were seen to decrease with attendant formation of significant quantities of ketones **4a** and **6**. As yet



uncharacterized carbonyl compounds were also produced in less significant quantities at 470–530°.

Characterization of **5** and particularly its differentiation from the remaining five isomers of cyclooctadienone was achieved in the following way. Firstly, the ketone exhibited a nonconjugated carbonyl absorption in the infrared at 1720 cm^{-1} (neat) and only end absorption in the ultraviolet region. Hydrogenation proceeded with the uptake of 2 equiv of hydrogen to give uniquely cyclooctanone. Ultimate structural confirmation was achieved by sodium borohydride reduction to alcohol **7**, whose ir and nmr spectra were identical with those of an authentic sample.[3]



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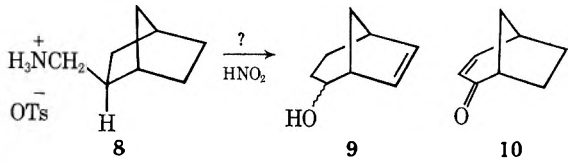
A possible unequivocal synthesis of **6** was suggested by the earlier work of Hall in which deamination of **8** was claimed to afford **9**.[4] However, repetition of

(1) National Science Foundation Graduate Trainee, 1970–1972.

(2) L. A. Paquette, G. V. Meehan, R. P. Henzel, and R. F. Eizember, *J. Org. Chem.*, **38**, 3250 (1973).

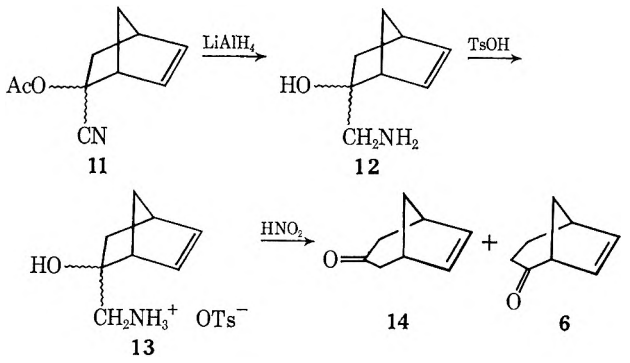
(3) P. Radlick and S. Winstein, *J. Amer. Chem. Soc.*, **86**, 1866 (1964). We thank Professor Radlick for making copies of these spectra available to us.

(4) H. K. Hall, *J. Amer. Chem. Soc.*, **82**, 1209 (1960).



8 9 10

this reaction and oxidation of the resulting mixture of alcohols gave, in our hands, very complex mixtures which presumably contain the isomeric ketone **10** as the major component. To avoid the operation of multiple carbonium ion rearrangements such as take place during this Tiffeneau ring expansion, recourse was made to the Demjanov–Tiffeneau procedure. Accordingly, acetoxy nitrile **11**,[5] obtained by the Diels–Alder reaction of cyclopentadiene and α-acetoxyacrylonitrile according to Bartlett,[6] was reduced with lithium aluminum hydride and converted to the tosylate salt **13** in conventional fashion. Nitrous acid deamination led to a 45:55 mixture of **14** and **6** which was separated



11 12 13 14 6

by preparative vpc methods. The less abundant isomer was identified by comparison of spectra and melting point with those of authentic material;[7] the major component proved identical with **6** in all respects.[8]

Ketones **4a** and **6** were stable to the pyrolysis conditions. Interestingly, however, **5** undergoes partial reversion to **3a** and irreversible conversion to **4a** and **6** in the temperature range studied (Table II).

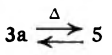


TABLE II

PYROLYSIS OF 5 AT VARIOUS TEMPERATURES

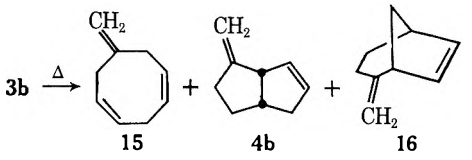
	Pyrolysate composition, %				
Temp, °C	5	3a	4a	6	Unknown
352	93	5			2
390	92	7			1
470	64	5	9	13	8

When related diene **3b** was heated under analogous conditions, similar thermal interconversions were observed (Table III). In this instance, rearrangement to bicyclic isomers occurred at somewhat lower temperatures than in the case of **3a**. The nmr spectrum of **15** shows many similarities to that of **5** and, in particular, reflects the symmetry inherent in the molecule. Its catalytic hydrogenation afforded only methylcyclooctane. Authentic **16** was synthesized by the action of methylenetriphenylphosphorane on **6**.

TABLE III

PYROLYSIS DATA OF 3b AT VARIOUS TEMPERATURES

	Pyrolysate composition, %				
Temp, °C	3b	15	4b	16	Unknown
365	88	11	0.5	0.5	
405	61	35	2	1	1
450	35	52	8	5	1
495	8	24	39	27	2
530	6	18	42	31	3
575		3	54	40	3



15 4b 16

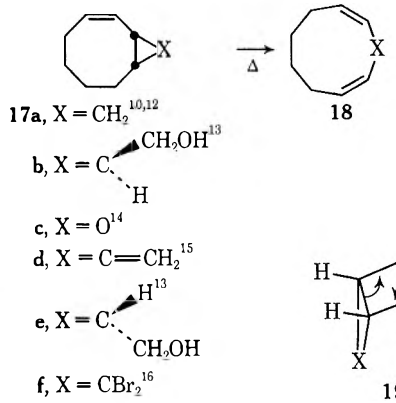
As revealed by the data in Table IV, 7-methylene-1,4-cyclooctadiene (**15**) also exists in thermal equilibrium with **3b** and is isomerized to **4b** and **16**. The latter two hydrocarbons proved stable over the entire range of temperatures examined.

TABLE IV

PYROLYSIS DATA OF 15 AT 455°

	Pyrolysate composition, %				
Temp, °C	15	3b	4b	16	Unknown
455	69	21	5	4	1

That electrocyclic opening of the cyclopropane ring in **3a** and **3b** which gives rise to **5** and **15**, respectively, follows a precedented 1,5-homodienyl hydrogen shift pathway elucidated initially by Doering[10] and Winstein,[11] and generalized in a number of subsequent investigations.[12–15] For example, to the extent that 9-substituted *cis*-bicyclo[6.1.0]non-2-ene derivatives carry no endo substituent at C_9 (*i.e.*, **17a–d**), concerted 1,5-hydrogen migration seemingly operates and the involvement of the unfavorable "saddle" conformation (**19**)



(5) Previously reported to consist of 75% exo acetate and 25% endo acetate: W. L. Dilling, R. D. Kroening, and J. C. Little, *J. Amer. Chem. Soc.*, **92**, 928 (1970).

(6) P. D. Bartlett and B. E. Tate, *J. Amer. Chem. Soc.*, **78**, 2473 (1956).

(7) N. A. LeBel and R. N. Liesemer, *J. Amer. Chem. Soc.*, **87**, 4301 (1965).

(8) Subsequent to our completion of this synthesis, LeBel[9] has described a more lengthy and involved route to this ketone. Although their reported ir and nmr spectra compare very closely with those of our material, their cited melting point (65–81°) indicates the obtention of a less pure sample by these workers.

(9) N. A. LeBel, N. D. Ojha, J. R. Menke, and R. J. Newland, *J. Org. Chem.*, **37**, 2896 (1972).

(10) W. von E. Doering and W. R. Roth, *Angew. Chem.*, **75**, 27 (1963); *Angew. Chem., Int. Ed. Engl.*, **2**, 115 (1963).

(11) D. S. Glass, J. Zirner, and S. Winstein, *Proc. Chem. Soc.*, 276 (1963); P. Radlick and S. Winstein, *J. Amer. Chem. Soc.*, **85**, 344 (1963).

(12) D. S. Glass, R. S. Boikess, and S. Winstein, *Tetrahedron Lett.*, 999 (1966).

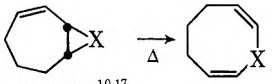
(13) D. L. Garin, *J. Amer. Chem. Soc.*, **92**, 5254 (1970).

(14) J. K. Crandall and R. J. Watkins, *Tetrahedron Lett.*, 1717 (1967).

(15) P. Radlick, W. Fenical, and G. Alford, *Tetrahedron Lett.*, 2707 (1970).

has been strongly implicated.[11,12] When attainment of this conformation is inhibited for steric reasons, as in the case of **17e** and **17f**, this rearrangement pathway is not followed.[13,16]

The less flexible *cis*-bicyclo[5.1.0]oct-2-ene systems (**20**) find it more energetically demanding to attain the requisite favored conformation and, although they do undergo bond reorganization to **21**, isomerization is less facile. Energies of activation for several re-



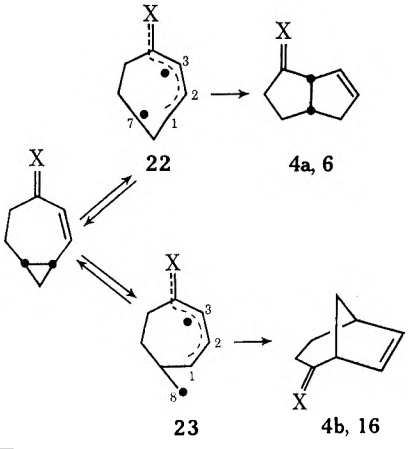
20a, X = CH_2[10,17]
b, X = CD_2[17]
c, X = O[14]

21

arrangements of this type have been determined and those associated with **17a** (E_a = 31.4 kcal/mol[12]) and **20a** (E_a = 38.6 kcal/mol[17]) illustrate the point clearly. In a number of examples, as in the present situation, this 1,5-hydrogen shift has been found to be reversible, the equilibrium lying heavily in favor of the monocyclic valence isomer. In flow systems such as the one employed herein, equilibrium is not achieved and, consequently, the data in Tables I–IV serve only as an indication of relative stabilities.

The current situation is further complicated at the more elevated temperatures by the incursion of two additional reactions, both of which are of the vinylcyclopropane–cyclopentene type. That these pathways are encountered only upon considerable thermal activation is consistent with the higher activation energies generally observed for such rearrangements (45–55 kcal/mol).[18] Were orbital symmetry factors in control of these 1,3 shifts a [$_\pi 2_a + {}_\sigma 2_s$] or [$_\pi 2_s + {}_\sigma 2_a$] process would necessarily operate. These transformations would give either a trans-fused [3.3.0] bicyclic containing a cis double bond or a cis-fused product containing a trans double bond. Neither of these results because of prohibitive strain, and biradicals are assumed to intervene.

The data require that the cyclopropane ring in **3a** and **3b** undergo homolytic scission in two ways in competitive fashion.[19] Rupture of the internal cyclopropane bond leads to **22**, which may return to starting material by C_1–C_7 bonding or proceed to **4a** or **6** upon C_3–C_7 bond formation. Similarly, biradical **23** can experience reclosure to the [5.1.0] bicyclic or cyclization to **4b** or **16**. The formation of comparable amounts of both product types may signal control of reactivity by a composite of conformational, steric, and electronic effects. It will be seen below that this apparently delicate balance of factors which exists with *cis*-bicyclo[5.1.0]oct-2-enes may be readily disrupted.



22 **4a, 6**

23 **4b, 16**

***cis*-Bicyclo[5.1.0]oct-5-enes 1a and 1b and Their [6.1.0] Bicyclic Homologs.**—When **1a** was heated at 500° for ≤3 sec in the flow system, a product mixture composed of **1a** and **2a** (ratio 3:1) was obtained (95% mass balance). An increase in temperature to 550° under the same conditions led to greater than 98% conversion to **2a**. At 600°, no **1a** remained and **2a** was the only volatile product isolated (50% yield). A point of interest was the observation that hydrocarbon **1b** likewise rearranges exclusively to **2b** but with a facility greater than its ketone counterpart. At 500°, for example, the clear pyrolysate consisted of 20% of **1b** and 80% of **2b** (85% mass balance). At 550°, vpc analysis of the reaction mixture showed it to be free of any unrearranged **1b**.

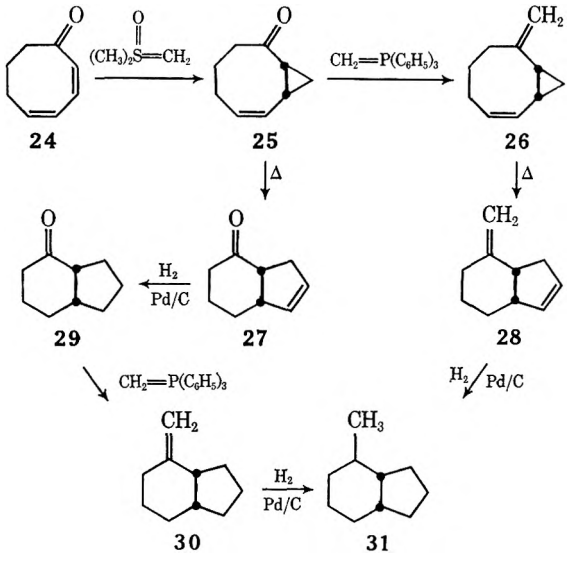
To extend the range of these transformations and demonstrate the general nature of the vinylcyclopropane rearrangement leading to ring-contracted (n − 2) products, the present work was broadened to include **25** and **26**. *cis*-Bicyclo[6.1.0]non-6-en-2-one (**25**) was synthesized in 80% yield from 2,4-cyclooctadien-1-one (**24**)[20] by reaction with dimethyloxosulfonium methylide. The spectral properties of **25** and methylene derivative **26** which are detailed in the Experimental Section serve to establish their gross structure. Pyrolysis of **25** at 600° resulted in only 10% conversion to a single isomeric product subsequently shown to be **27** on the basis of spectra and hydrogenation to *cis*-bicyclo[4.3.0]nonan-2-one (**29**).[21] At more elevated temperatures (Table V), the conversion to **27** could be enhanced somewhat. At 700°, however, significant competitive decomposition began to set in. By way of contrast, **26** underwent 98% conversion to **28** at 600° (92% mass recovery). The structure assigned to the product diene was confirmed by hydrogenation to **31** and independent synthesis of this same hydrocarbon from **29** (see scheme).

TABLE V
PYROLYSIS OF 25 AT VARIOUS TEMPERATURES

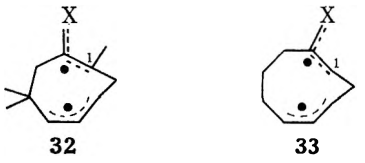
	Pyrolysate composition, %		
Temp, °C	**25**	**27**	Unknowns
600	90	10	
650	67	33	
700	70	17	13

The greater ease of rearrangement of **1a** and **1b** relative to **25** and **26** is not reconcilable with the increased conformational flexibility of the [6.1.0] bicyclics. Past experimental experience provides evidence that less sterically constrained systems generally rearrange more smoothly, particularly when a concerted migration is

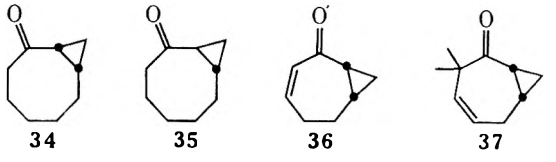
(16) M. S. Baird, D. G. Lindsay, and C. B. Reese, *Chem. Commun.*, 784 (1968).
(17) W. Grimme, *Chem. Ber.*, **98**, 756 (1965).
(18) W. von E. Doering and E. K. G. Schmidt, *Tetrahedron*, **27**, 2005 (1971).
(19) This conclusion is warranted since **4a**, **6**, **4b**, and **16** are produced irreversibly at the temperatures employed.
(20) A. C. Cope, S. Moon, C. H. Park, and G. L. Woo, *J. Amer. Chem. Soc.*, **84**, 4865 (1962).
(21) L. A. Paquette, D. E. Kuhla, and J. H. Barrett, *J. Org. Chem.*, **34**, 2879 (1969); W. Hückel and E. Goth, *Chem. Ber.*, **67**, 2104 (1934).



involved.[10,12,14] The apparently lower energies of activation for **1a** and **1b** are therefore presented as evidence for biradical intervention, the additional methyl substitution at C_1 in **32** providing additional

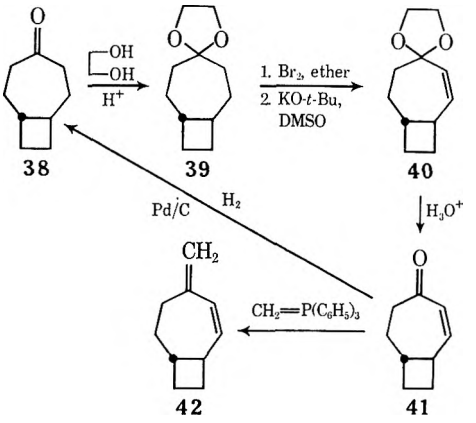


transition-state stabilization. The development of allylic radical character in these intermediates is of maximum import as gauged from the complete inertness of ketones **34–37** to thermal activation, even at temperatures as high as 650°.[22]



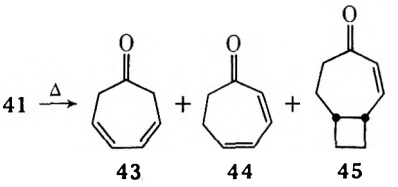
trans-**Bicyclo[5.2.0]non-2-enes 41 and 42.**—At this point, attention was turned to medium-ring compounds containing a vinylcyclobutane moiety. Despite the failure of *trans*- and *cis*-bicyclo[5.2.0]non-2-ene derivatives to undergo novel excited-state isomerization reactions,[2] the growing number of stereochemically fascinating thermally promoted vinylcyclobutane rearrangements dictated that the response of these molecules to heat be examined.[24]

The synthesis of trans-fused ketone **41** was achieved in four steps by application of the Garbisch procedure[25] to the known saturated ketone **38**.[26] To rule out possible epimerization of the trans-fused ring fusion during this reaction sequence, the α,β-unsaturated ketone so produced (**41**) was catalytically hydrogenated. Starting ketone **38** was produced uncontaminated by the presence of the cis isomer in full support of the indicated structural assignment. For the preparation of **42**, the



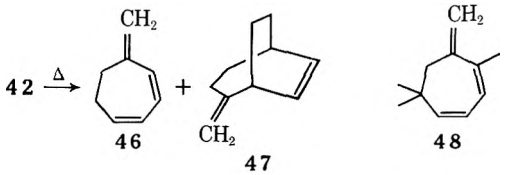
Wittig reaction was again employed. A homogeneous hydrocarbon (**42**) was produced which was distinctly different from the cis isomer (see below). Therefore, although Wittig conditions do frequently serve to induce epimerization, the possibility of trans → cis isomerization in this case may be dismissed.

Upon being heated at 500° in the flow system, ketone **41** underwent 50% conversion to a mixture of 3,5-cycloheptadienone (**43**, 15%), 2,4-cycloheptadienone (**44**, 18%), and the cis isomer **45** (14%). Independent



synthesis of **43** was achieved by lithium aluminum hydride reduction of tropone.[27] Thermal activation of **43** results in partial equilibration with **44**[28] from which it is readily separated by vpc techniques. The cis [5.2.0] bicyclic ketone **45** was identified by comparison with authentic material (see below). Pyrolysis at higher temperatures resulted in the formation of more volatile secondary products and heating at lower temperatures resulted simply in lower conversion to the three indicated ketones.

The thermolysis of **42** at 500° (25 mm) led to the formation of two major products amounting to 73 and 18% of the volatile material. A plethora of minor components comprised the remaining 9% and these remain uncharacterized. The possibility that the major substance was triene **46** was suggested by its greatly reduced vpc retention time, ultraviolet spectrum [$\lambda_{max}^{isooctane}$ 283 nm (ϵ 16,000)] which compares very favorably with that reported for **48** [$\lambda_{max}^{C_2H_5OH}$ 287 nm (log ϵ 4.04)],[29]



(22) Subsequent to completion of this particular phase of our work, Crandall and Watkins[23] have shown that 3- and 4-cyclooctenone do rearrange thermally at 720°.

(23) J. K. Crandall and R. J. Watkins, *J. Org. Chem.*, **36**, 913 (1971).

(24) Consider, for example, the following reports: J. A. Berson and G. L. Nelson, *J. Amer. Chem. Soc.*, **89**, 5303 (1967); W. R. Roth and A. Friedrich, *Tetrahedron Lett.*, 2607 (1969); F. Scheidt and W. Kirmse, *Chem. Commun.*, 716 (1972); E. Vogel, *Justus Liebigs Ann. Chem.*, **615**, 1 (1958).

(25) E. W. Garbisch, Jr., *J. Org. Chem.*, **30**, 2109 (1965).

(26) N. L. Allinger, M. Nakazaki, and V. Zalkow, *J. Amer. Chem. Soc.*, **81**, 4047 (1959).

(27) O. L. Chapman, D. J. Pasto, and A. A. Griswold, *J. Amer. Chem. Soc.*, **84**, 1213 (1962).

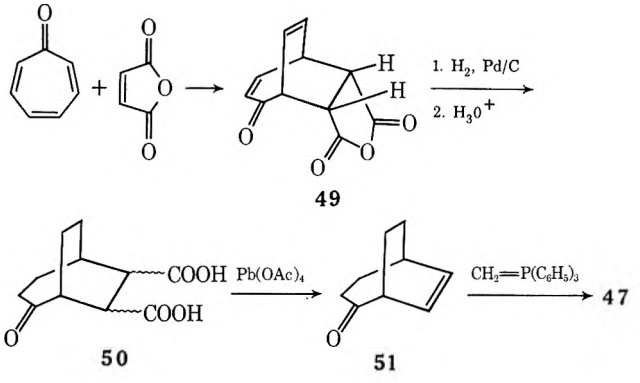
(28) A. P. ter Borg and H. Kloosterziel, *Recl. Trav. Chim. Pays-Bas*, **82**, 1189 (1963).

(29) K. Conrow, *J. Amer. Chem. Soc.*, **83**, 2958 (1961).

and nmr features. Methylene-2,4-cycloheptadiene (**46**) was then prepared independently by subjecting the thermally equilibrated mixture of **43** and **44** to the Wittig reaction. Somewhat surprisingly, it was found that **43** does not react with methylenetriphenylphosphorane under the usual conditions, whereas **44** is essentially completely converted to **46**. The widely differing reactivity of these ketones permitted facile separation of **46**.

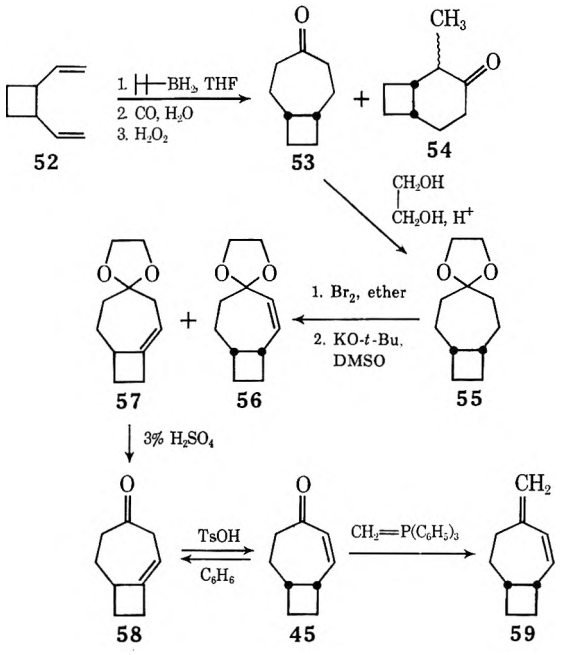
In confirmation of the structural assignment to **47**, a Wittig reaction on **51** was effected. Although this ketone had previously been synthesized by Berson and Jones,[30] it proved more convenient to obtain this substance in quantity from diacid **50** which is readily available from the Diels–Alder reaction of tropone and maleic anhydride.[31] Oxidative bisdecarboxylation of **50** with lead tetraacetate[32] proceeded in acceptable yield (39%).

cis-**Bicyclo[5.2.0]non-2-enes 45 and 59.**—Synthesis of saturated ketone **53** along the lines previously developed[26] is not only more difficult than that of its trans



isomer, but is beset by exceedingly poor yields at one step. Accordingly, a new, rapid, and improved preparation of **53** was developed starting with the readily available *cis*-1,2-divinylcyclobutane (**52**).[33,34] Purified **52** was treated with thexylborane and then carbonylated at approximately 1000 psi of carbon monoxide in the presence of water according to the procedure developed by Brown and Negishi.[35] After oxidative work-up, there was obtained in 27% yield a 75:25 mixture of ketones identified as **53** and **54**. The latter product presumably arises as a result of thexylborane addition to the internal position of one of the vinyl groups *via* a six-center transition state. Although **53** and **54** are separable by efficient distillation, in practice it proved more convenient to ketalize the mixture directly and to isolate **55** at this stage.

Some difficulties were encountered in introducing the requisite unsaturation. When **55** was brominated and subsequently treated with potassium *tert*-butoxide in dimethyl sulfoxide solution, incomplete dehydro-



bromination took place. When somewhat more forcing conditions were employed, some isomerization to **57** was noted. Also, when unreacted bromo ketal was recycled, only **57** was obtained. These results suggest that two different monobromides are produced, one of which dehydrobrominates with sufficient reluctance that base-catalyzed double bond isomerization accompanies the process.

Upon hydrolysis of **57**, only β,γ-unsaturated ketone **58** was isolated. When heated at reflux in benzene solution containing *p*-toluenesulfonic acid for several hours,[36] an equilibrium distribution consisting of 43% of **58** and 57% of **45** was attained. Clearly, the cis-fused bicyclo[5.2.0]nonen-4-one system finds little stabilization to be gained by conjugation perhaps as a consequence of adverse conformational and steric factors. The difference in chemical shifts of the α and β protons in **45** (28 Hz) indicates the absence of significant conjugative overlap with the carbonyl group compared to a highly conjugated ketone like 2-cyclopentenone ($\nu_a - \nu_b$ = 101.5 Hz).[36] These same factors are less evident in trans isomer **41** for which $\nu_a - \nu_b$ = 54 Hz.

Submission of **45** to thermolysis at various temperatures afforded varying quantities of bicyclo[3.2.2]non-6-en-2-one (**51**) and cycloheptadienones **43** and **44** (Table VI). Since it was of paramount interest to deter-

TABLE VI
PYROLYSIS OF **45** AT VARIOUS TEMPERATURES

	Pyrolysate composition, %				
Temp, °C	**45**	**51**	**43**	**44**	Unknowns
385	96	2			2[a]
430	78	6	6	5	5
490	18	22	21	24	15[b]
555	5	42	11	5	37[b]

[a] Present in starting material. [b] A considerable amount of this material consists of low-boiling products.

mine whether *cis*-3a,4,5,7a-tetrahydro-1-indanone (**60**) was produced in this reaction, this previously unknown ketone was synthesized. To this end, the photoisomerization of **51** was studied in the expectancy that

(30) J. A. Berson and M. Jones, Jr., *J. Amer. Chem. Soc.*, **86**, 5017, 5019 (1964).

(31) T. Nozoe, T. Mukai, T. Nagese, and Y. Toyooka, *Bull. Chem. Soc. Jap.*, **33**, 1247 (1960).

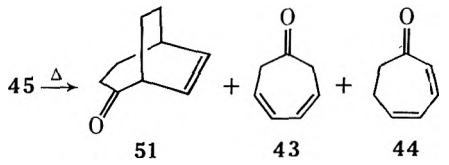
(32) C. M. Cimarusti and J. Wolinsky, *J. Amer. Chem. Soc.*, **90**, 113 (1968).

(33) P. Heimbach and W. Brenner, *Angew. Chem., Int. Ed. Engl.*, **6**, 800 (1967); *Angew. Chem.*, **79**, 813 (1967); W. Brenner, P. Heimbach, H. Hey, E. W. Müller, and G. Wilke, *Justus Liebigs Ann. Chem.*, **727**, 161 (1969); G. S. Hammond, N. J. Turro, and R. S. H. Liu, *J. Org. Chem.*, **28**, 3297 (1963).

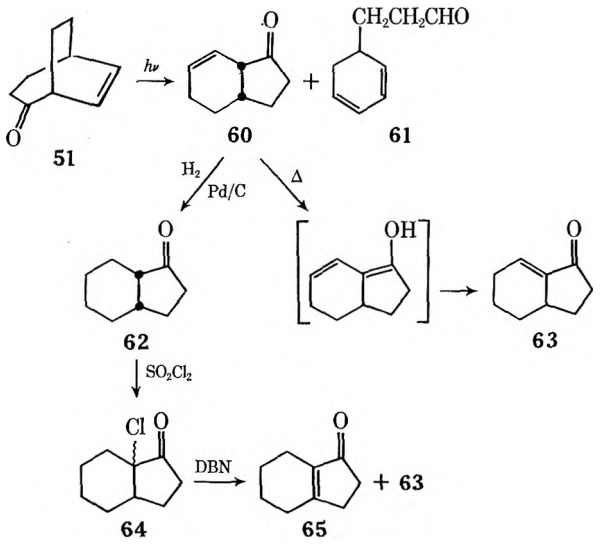
(34) We thank Dr. Paul Heimbach and the Max Planck Institut für Kohlenforschung for providing us with a generous supply of **52**.

(35) H. C. Brown and E. Negishi, *J. Amer. Chem. Soc.*, **89**, 5477 (1967); H. C. Brown and E. Nigishi, *Chem. Commun.*, 594 (1968).

(36) N. Heap and G. H. Whitham, *J. Chem. Soc. B*, 164 (1966).



its excited-state behavior would parallel that of norbornenone, which readily gives bicyclo[4.2.0]oct-2-en-8-one upon photolysis.[37] In point of fact, direct irradiation of **51** did result in facile 1,3-sigmatropic acyl shift with formation of **60** (85% yield). Less efficient conversion to aldehyde **61** (13%) was also operative. Any question that the ring system in **60** be of some other type was removed by its catalytic hydrogenation to *cis*-perhydroindanone (**62**). The location of the double bond was confirmed when it was discovered that passage of **60** through a gas chromato-



graphic column at temperatures in excess of 165° resulted in partial conversion to the conjugated isomer **63**. The hypothetical dienol is seemingly the significant intermediate in this interconversion. Authentic **63** was obtained as the minor product from the chlorination–dehydrochlorination of **62**.[38]

The ultraviolet spectrum of **61** is that of a simple 1,3-cyclohexadiene chromophore [$\lambda_{max}^{cyclohexane}$ 260 nm (ϵ 5000)].[39] In addition, its nmr spectrum features four olefinic protons (δ 5.5–6.1) and a low-field triplet centered at δ 9.84 (J = 1.5 Hz) characteristic of a $-CH_2CHO$ functional group. The presence in **61** of these structural parameters typifies the substance as the result of well-precedented[40] Norrish type I cleavage of **51** followed by intramolecular hydrogen abstraction.[41]

The results obtained from gas-phase pyrolysis of **59** at 390–555° (Table VII) are seen to be very similar

(37) R. S. Givens, W. F. Oettle, R. L. Coffin, and R. G. Carlson, *J. Amer. Chem. Soc.*, **93**, 3957 (1971); R. S. Givens and W. F. Oettle, *ibid.*, **93**, 3963 (1971).

(38) The procedure employed was patterned after that employed in the 1-decalone series: H. O. House and H. W. Thompson, *J. Org. Chem.*, **26**, 3729 (1961).

(39) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N. Y., 1967, pp 157–158.

(40) For a recent discussion of the mechanism of this type of photochemical reaction, see H. Sato, N. Furutachi, and K. Nakanishi, *J. Amer. Chem. Soc.*, **94**, 2150 (1972).

(41) For another recent example, note J. Meinwald and R. A. Chapman, *J. Amer. Chem. Soc.*, **90**, 3218 (1968).

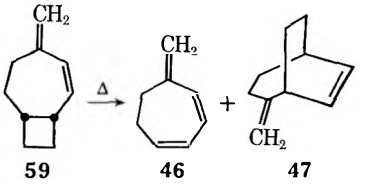
TABLE VII

PYROLYSIS OF **59** AT VARIOUS TEMPERATURES

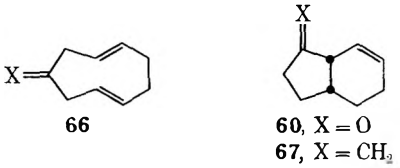
	Pyrolysate composition, %			
Temp, °C	**59**	**46**	**47**	Unknowns
390	99	0.5		0.5
430	88	7	3	2
465	53	31	13	2
505	15	59	21	5[a]
555	3	68	20	9[a]

[a] The major constituents are low-boiling substances.

to those realized from heating of the trans isomer **42** with **46** and **47** arising as the major products.



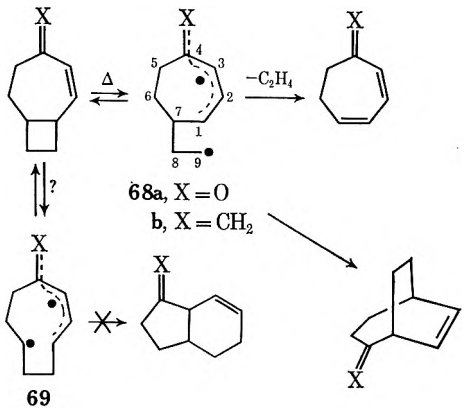
These experimental data can now be contrasted with those from the rearrangement of the [5.1.0] bicyclics **3a** and **3b**. Whereas a 1,5-homodienyl shift is easily effected in the low-temperature pyrolysis of the cyclopropyl compounds, none of the corresponding products **66** (no stereochemical implication intended) is observed from either stereoisomeric cyclobutane series. Furthermore, whereas significant amounts of material arising from 1,3 migration of the internal cyclopropyl bond in **3a** and **3b** are formed at the higher temperatures studied, no evidence was gained for the production of either **60** or **67** upon thermal activation of the [5.2.0]

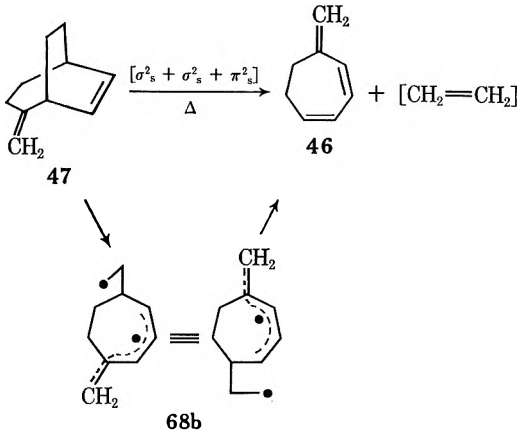


bicyclics. Rather, the experimental observations realized from heating of the various vinylcyclobutanes can be most economically explained in terms of rupture of the external C_1–C_9 bond of the four-membered ring with formation of stabilized biradicals of type **68**. Continuation of the bond-breaking process leads to the loss of ethylene, while radical recombination either returns the original carbon framework (with or without loss of stereochemistry) or leads to [3.2.2] bicyclic product (see scheme). There exists no need to postulate the intervention of biradicals such as **69**. Should central bond homolysis occur in these systems, however, it is clear that rebonding to produce less strained [4.3.0] bicyclics does not operate.

Control experiments conducted on **60** have shown that at 490° the material is recovered 90% unchanged. At 555°, 62% of the unreacted ketone was returned. In both instances, isomerization to **63** was the only process in evidence. Consequently, if **60** had been formed during the pyrolysis of **41** and **45**, major amounts of this substance would have been easily detected.

In contrast to the proclivity of cis ketone **45** for isomerization to bicyclo[3.2.2]non-6-en-2-one (**51**), trans isomer **41** gives no comparable vinylcyclobutane rearrangement product. It is easily seen from Dreiding molecular models that the rigid and highly puckered framework of the trans-fused system precludes facile





approach of C_9 to C_3 (see **68**) in a suprafacial shift unless simultaneous pivoting about the C_1–C_7, C_6–C_7, and C_7–C_8 σ bonds also obtains. Without the benefit of these ancillary motions, the hydrogen at C_7 would be prohibitively forced into the interior of the molecule. In this context, it is not surprising that C_1–C_9 recombination of the 1,4-butanediyl (with or without inversion of configuration) proceeds faster than more deep-seated skeletal changes. Since the reluctance toward 1,3 shift is an apparent consequence of the trans-fused cyclobutane ring in **41**, elimination of this barrier as in cis isomer **45** removes the obstacle for rearrangement. That the **45** produced *in situ* during the pyrolysis of **41** undergoes no further isomerization is a reflection of the quite short contact time.

The similarity of results for **42** and **59** may reflect a greater lifetime for biradical **68b** relative to **68a** as they originate from trans-fused precursors. A longer lifetime for the hydrocarbon species would allow for conformational readjustments necessary for ultimate isomerization to **47**. The possibility also remains that **42** suffers initial rearrangement to **59** which in turn experiences yet more rapid conversion to **47**.

Lastly, we call attention to the fact that concerted thermal extrusion of ethylene from the four [5.2.0] bicyclics could proceed in the $[{}_\sigma 2_a + {}_\sigma 2_s]$ mode. Disregarding for the moment the attractiveness of the diradical mechanism, we point out that postulation of such concerted cleavage reactions actually leads to inaccurate predictions. Since simultaneous rupture of two diametrically opposed cyclobutane bonds in a + s fashion requires extensive twisting of the four-membered ring in the transition state, then loss of ethylene should be more facile than isomerization in the trans series where the cyclobutane is already markedly contorted. However, the combined experimental data are in contradiction with this proposal. In addition, whereas postulation of orbital symmetry control would necessitate the competitive operation of a second mechanism to explain the formation of isomerized compounds, a single biradical intermediate is able to account for all products.

Some measure of further support for the biradical process was derived from pyrolysis studies of **47**. When heated to 555° in the flow system, 10% conversion to **46** resulted. One reasonable explanation of this observation is that **47** is also a source of biradical **68b**, which again is partitioned in the direction of ethylene loss and formation of **47**. This interpretation does not uniquely accommodate the facts, however, since a retro Diels–Alder pathway also serves to explain this observation. In this connection, the related ketone **51** was found not to fragment ethylene at 555°.

Summary.—In conclusion, it is to be noted that cis-[5.1.0] bicyclics exhibit thermal rearrangement chiefly by two pathways. The first of these is the vinylcyclopropane–cyclopentene bond reorganization and, indeed, ring contraction by 1,3 shift of the *internal* cyclopropane bond is followed exclusively by **1**. Isomerization to a less strained bicyclic system by vinylcyclopropane rearrangement involving an *external* cyclopropyl bond is of significance in the case of **3**. However, the 1,5-homodienyl hydrogen shift process which gives rise to a 1,4-cyclooctadiene derivative is now seen to be a competitive reaction. No 1,3 shift of the *internal* cyclobutane bond was evidenced in the thermal behavior of the several cis and trans [5.2.0] bicyclics studied. Allylic rearrangement of an *external* cyclobutane bond to afford [3.2.2]bicyclic products does operate in certain examples, but the major pathway is fragmentation with loss of ethylene and formation of cycloheptadiene systems.

Experimental Section

General.—Melting points are corrected. Proton magnetic resonance spectra were obtained with a Varian A-60A spectrometer and apparent coupling constants are cited. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

Compounds were pyrolyzed in a flow system consisting of a 28 cm × 16 mm quartz tube packed with quartz chips heated in a 12-in. furnace. Samples were introduced by volatilization (usually at 20–30 mm) into a slow stream of nitrogen (flow *ca.* 1 ml/min) and products were collected in a U tube cooled in a Dry Ice–isopropyl alcohol bath. For analytical runs, 2–3-mg samples were pyrolyzed, collected, diluted with an inert solvent such as ether or pentane, and analyzed by vpc methods. The percentage composition of mixtures was determined by manual integration of vpc traces. Final purification of samples was accomplished by preparative vpc unless otherwise noted. All vpc columns employed were constructed of 0.25-in. Al tubing and, except where noted, liquid phases were coated on 60–80 mesh Chromosorb G: A, 12 ft, 5% XF-1150; B, 6 ft, 5% QF-1; C, 12 ft, 5% SF-96; D, 12 ft, 5% SE-30; E, 6 ft, 20% AF-1 packed on 60–80 mesh Chromosorb W; F, 6 ft, 5% SE-30; G, 6 ft, 5% SF-96; H, 7 ft, 6% AF-1; I, 6 ft, 5% XF-1150; J, 6 ft, 5% Carbowax 2000M.

Thermal Isomerization of *cis*-Bicyclo[5.1.0]oct-2-en-4-one (3a).—Pyrolysis of **3a**[2] at various temperatures gave the result summarized in Table I. Analyses were performed with column A at 150°. The first compound to elute was identified as *cis*-bicyclo[3.3.0]oct-7-en-2-one (**4a**) by comparison of spectra with those of an authentic sample.[2,42] Bicyclo[3.2.1]oct-6-en-2-one

(42) L. A. Paquette, G. V. Meehan, and R. F. Eizember, *Tetrahedron Lett.*, 995 (1969).

(6) was the second compound eluted; this ketone was identical with a sample prepared in unambiguous fashion (see below). 3,6-Cyclooctadienone (5), the third component collected, had the following spectral properties: ν_{max}^{neat} 1720 cm^{-1}; $\lambda^{isooctane}$ end absorption; $\delta_{TMS}^{CDCl_3}$ 5.78 (m, 4, olefinic), 3.18 (d, J = 4.0 Hz, 4, $-CH_2CO-$), and 2.78 (m, 2, doubly allylic protons); calcd m/e 122.0732, found 122.0729.

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: 78.25; H, 8.19.

Recovered **3a** was the last material to elute from the column.

Hydrogenation of 5.—A 23.6-mg sample of **5** dissolved in 3.5 ml of anhydrous ether was hydrogenated over 10 mg of 5% Pd/C for 3 hr at atmospheric pressure. The catalyst was separated by filtration, the solution was concentrated in a stream of nitrogen, and the lone product was isolated by preparative vpc on column B at 120°. There was obtained 15.5 mg of cyclooctanone.

3,6-Cyclooctadienol (7).—To a solution of 30 mg of **5** in 2 ml of absolute methanol cooled to 5° was added 95 mg (tenfold excess) of sodium borohydride. The solution was stirred for 2 hr while gradually warming to room temperature. Pentane and saturated sodium chloride solution were added and the layers were separated. The aqueous phase was extracted several times with additional pentane and the combined organic layers were dried and evaporated to give 20 mg of crude **7**. Molecular distillation at 60° (15 mm) afforded pure **7**, identical in all respects with an authentic sample.[3]

Alternate Synthesis of Bicyclo[3.2.1]oct-6-en-2-one (6). A. 2-(2-Hydroxybicyclo[2.2.1]hept-5-enyl)methylamine (12).—To a refluxing stirred slurry of 3.80 g (0.10 mol) of lithium aluminum hydride in 100 ml of anhydrous ether was added over a period of several hours a solution of 8.85 g of **11**[6] in 35 ml of dry ether. The mixture was heated at reflux overnight and treated sequentially with 4 ml of water, 4 ml of 30% potassium hydroxide solution, and 10 ml of water with efficient ice-bath cooling. Usual processing was followed by distillation *in vacuo*, bp 81–83° (1.3 mm).

In a second identical run but without distillation, the ethereal solution of **12** was treated with 9.50 g (0.05 mol) of *p*-toluenesulfonic acid monohydrate dissolved in 100 ml of ether with ice cooling. After overnight storage at 0°, the precipitated solid was filtered. There was obtained 11.3 g (72% overall) of tosylate salt **13**. Recrystallization from methanol–chloroform and ethyl acetate–methanol (3:1) gave crystals: mp 172–172.5° dec; $\delta_{DSS}^{D_2O}$ 7.54 (AA'BB' q, 4, aromatic), 6.47 (m, 1, olefinic), 6.18 (m, 1, olefinic), 3.26 (br s, 2, $-CH_2N<$), 2.88 (br m, 2, bridgehead protons), 2.38 (s, 3, methyl), and 1.0–2.1 (br m, 4).

Anal. Calcd for $C_{15}H_{21}NO_4S$: C, 57.85; H, 6.80; N, 4.50. Found: C, 58.01; H, 6.75; N, 4.41.

B. Deamination of 13.—Tosylate **13** (11.2 g, 0.036 mol) was dissolved in 200 ml of cold water and 2.5 ml of acetic acid was added. A solution of 2.75 g (0.04 mol) of sodium nitrite in 25 ml of water was added, but no gas evolution was observed until the solution was warmed to 20–30°. After *ca.* 1 hr, 450 ml of nitrogen had been evolved and the solution became light yellow. An additional 3 ml of acetic acid and 2.50 g of sodium nitrate was added and the solution was stirred for several hours at room temperature. The product was extracted with ether (4 × 200 ml) and the combined organic layers were washed with saturated sodium bicarbonate and sodium chloride solutions. The majority of the solvent was distilled from the dried solution at atmospheric pressure and the residue was sublimed at 30 mm and 40–80° (bath temperature). The yield of white volatile solid was 1.10 g. Vpc analysis (column A at 150°) indicated a 55:45 ratio of **6** to **14**. Isolated **14** melted at 97.5–100° (lit.[7] mp 99–100.5°) and its ir and nmr spectra conformed to those in the literature report. Isolated **6** melted at 76.5–79° and was identical with the ketone isolated from the pyrolysis of **3a**: $\nu_{max}^{CHCl_3}$ 1717 cm^{-1}; $\delta_{TMS}^{CHCl_3}$ 6.15 (symmetrical eight-line pattern, 2, olefinic), and 1.6–3.1 (br m, 8).

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.29; H, 8.21.

Thermal Rearrangement of 4-Methylene-*cis*-bicyclo[5.1.0]oct-2-ene (3b).—Pyrolyses were conducted as previously described giving the results summarized in Table III. The products were analyzed and separated with the aid of column C at 110°. 2-Methylenebicyclo[3.2.1]oct-6-ene (**16**) was eluted first and showed ir and nmr spectra identical with those of the authentic sample prepared below. The second component proved to be 8-methylene-*cis*-bicyclo[3.3.0]oct-2-ene (**4b**).[42] The third compound was 7-methylene-1,4-cyclooctadiene (**15**): $\delta_{TMS}^{CDCl_3}$ 5.60 (symmetrical ten-line multiplet, 4, ring vinyls), 4.79 (m, 2, terminal methylene), 2.95 (m, 6, bisallylic protons).

Anal. Calcd for C_9H_{12}: C, 89.94; H, 10.06. Found: C, 89.82; H, 9.98.

Unchanged **3b** emanated last from this column.

Hydrogenation of 15.—Triene **15** (21.9 mg) dissolved in 5 ml of ether was hydrogenated over 20 mg of 10% Pd on carbon until hydrogen uptake was complete. The mixture was filtered through a short column of Celite and the filtrate was carefully concentrated. The hydrocarbon isolated upon vpc purification (column C, 110°) exhibited ir and nmr features identical with those of methylcyclooctane.

2-Methylenebicyclo[3.2.1]oct-6-ene (16).—An impure sample of **6** dissolved in dry ether was heated at reflux overnight under nitrogen in the presence of excess methylenetriphenylphosphorane. After cooling, water was added and the mixture was extracted with pentane. The solvent was carefully removed and the resulting diene **16** was isolated from column C at 110°: $\delta_{TMS}^{CDCl_3}$ 5.93 (m, 2, ring vinyls), 3.03 (dd, 2, terminal methylene), 2.6 (m, 1), 1.7–2.4 (m, 3), and 1.3–1.7 (m, 3).

Anal. Calcd for C_9H_{12}: C, 89.94; H, 10.06. Found: C, 90.20; H, 10.02.

This hydrocarbon was identical with that isolated above from the pyrolysis of **3b**.

Pyrolysis of 1,4,4-Trimethyl-*cis*-bicyclo[5.1.0]oct-5-en-2-one (1a).—An 82-mg sample of **1a**[43] was pyrolyzed at 550° (10 mm) as before. Molecular distillation [50° (10 mm)] afforded 65 mg (81%) of a colorless liquid, vpc analysis of which on column G at 115° showed the material to contain less than 1% of **1a** and to be otherwise homogeneous. The isolated product was identical with **2a** in all respects.

Pyrolysis of 2-Methylene-1,4,4-trimethyl-*cis*-bicyclo[5.1.0]oct-5-ene (1b).—An 81-mg sample of **1b**[2] was pyrolyzed in the usual manner at 550° (10 mm). Molecular distillation at 50° (10 mm) of the collected product gave 61 mg (70%) of a colorless liquid homogeneous of vpc (column G, 115°). This hydrocarbon was identical with authentic **2b**.[2]

***cis*-Bicyclo[6.1.0]non-6-en-2-one (25).**—A mixture of 0.03 mol of oil-free sodium hydride and 7.0 g (0.03 mol) of trimethyloxosulfonium iodide in 50 ml of dry dimethyl sulfoxide was stirred under nitrogen at room temperature for 30 min. A solution of 3.6 g (0.03 mol) of freshly distilled 2,4-cyclooctadienone (**24**)[20] in 20 ml of dimethyl sulfoxide was added and stirring was maintained for 2 hr. The solution was poured into 100 ml of water and extracted with ether. The combined organic layers were dried, filtered, and evaporated. Fractionation of the residual oil afforded 3.4 g (80%) of **25**: bp 85–86° (2 mm); ν_{max}^{neat} broad carbonyl absorption at 1750–1700 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.6 (m, 2, olefinic) and 1.0–2.7 (m, 10).

The semicarbazone melted at 165–166°.

Anal. Calcd for $C_{10}H_{15}N_3O$: C, 62.15; H, 7.82; N, 21.75. Found: C, 62.20; H, 7.91; N, 21.43.

2-Methylene-*cis*-bicyclo[6.1.0]non-6-ene (26).—To a suspension of 3.6 g (0.01 mol) of methyltriphenylphosphonium bromide in 50 ml of anhydrous ether under nitrogen was added dropwise 4.3 ml (0.011 mol, 1.6 M) of *n*-butyllithium in hexane and stirring was maintained for 3 hr. A solution of 1.34 g (0.01 mol) of **25** in 10 ml of ether was added dropwise and the resulting suspension was refluxed for 12 hr. Water (50 ml) was added, the ether layer was separated, and the aqueous layer was reextracted with ether. The ethereal layers were combined, washed with brine, dried, and carefully evaporated *in vacuo*. Pentane (50 ml) was added and the suspension was filtered. Concentration of the filtrate and distillation furnished 1.1 g (82%) of **26** as a colorless liquid: bp 76–78° (10 mm); $\delta_{TMS}^{CDCl_3}$ 5.5 (br s, 2, olefinic), 4.8 (s, 2, methylene protons), and 0.2–2.7 (br m, 10).

Anal. Calcd for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.28; H, 10.49.

Thermal Rearrangement of 25.—A 100-mg (0.7 mmol) sample of **25** was pyrolyzed in the flow system at 650° (10 mm) (contact time ≤3 sec). The collected product was molecularly distilled at 50° (10 mm) to give 84 mg (84%) of a clear liquid. Vpc analysis on column G showed the ratio of **25** to a single product to be 2:1. The new substance was isolated and was assigned structure **27**: ν_{max}^{neat} 1710 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.7 (m, 2, olefinic) and 1.2–3.4 (br m, 10). This ketone was not identical with either **60** or **63**.

(43) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 78.99; H, 9.03.

Hydrogenation of *cis*-Bicyclo[4.3.0]non-7-en-2-one (27).—To a solution of 25 mg (0.2 mmol) of **27** in 25 ml of hexane was added 4 mg of 10% palladium on carbon and hydrogenation was effected at atmospheric pressure for 2 hr (uptake of 4 ml of H_2). The mixture was filtered through Celite to remove the catalyst, concentrated, and subjected to vpc isolation (column G). There was obtained 16 mg (60%) of **29**, identical in all respects with an authentic sample.[21]

Thermal Rearrangement of 26.—A 100-mg sample (0.2 mmol) of **26** was pyrolyzed at 600° (10 mm) as previously described. Molecular distillation of the collected product at 50° (10 mm) yielded 92 mg (92%) of a colorless liquid, vpc analysis of which revealed the presence of >98% of a single product (**28**). Purification was effected by preparative isolation from column G: ν_{max}^{neat} 1645, 1440, 893, 884, and 705 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.8 (m, 2, olefinic), 4.17 (br s, 2, methylene protons), and 1.0–3.1 (br, 10).

Anal. Calcd for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.66; H, 10.45.

Hydrogenation of 2-Methylene-*cis*-bicyclo[4.3.0]non-7-ene (28).—A solution of 67 mg (0.5 mmol) of **28** in 25 ml of hexane containing 5 mg of 5% palladium on carbon was hydrogenated at atmospheric pressure as before. Isolation of the product by preparative-scale vpc techniques yielded 57 mg (80%) of **31**, indicated in all respects with the authentic sample prepared below.

2-Methylene-*cis*-bicyclo[4.3.0]nonane (30).—Reaction of 3.5 g (0.001 mol) of methyltriphenylphosphonium bromide, 12 ml (0.001 mol) of 1.2 *M* *n*-butyllithium in hexane, and 91 mg of **29** in the predescribed fashion led to the isolation of 64 mg (80%) of **30**: ν_{max}^{neat} 1635, 1440, 1025, and 890 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 4.7 (br s, 2, methylene protons) and 0.9–2.7 (br, 14 H).

Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 87.91; H, 11.97.

2-Methyl-*cis*-bicyclo[4.3.0]nonane (31).—A solution of 41 mg (0.3 mmol) of **30** dissolved in 25 ml of hexane containing 5 mg of 5% palladium on carbon was hydrogenated as before at atmospheric pressure to give 32 mg (75%) of **31** after vpc isolation (column J): ν_{max}^{neat} 1450, 1375, and 1300 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 1.0–2.8 (br envelope).

Anal. Calcd for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 87.09; H, 13.05.

***trans*-Bicyclo[5.2.0]nonan-4-one Ethylene Ketal (39).**—To 5.48 g (0.0398 mol) of **38**[26] dissolved in 50 ml of benzene was added 100 mg of *p*-toluenesulfonic acid and 3.71 g (0.0597 mol) of ethylene glycol. The flask was fitted with a Dean–Stark trap and heated under reflux for 8 hr. At the end of this time, most of the benzene was removed at reduced pressure and 50 ml of ether was added. The mixture was washed with saturated sodium carbonate solution, and the aqueous layer was extracted with 25 ml of ether. The combined ether extracts were dried and distilled to give 6.23 g (86%) of ketal **39**: bp 79–82° (0.9 mm); $\delta_{TMS}^{CCl_4}$ 3.82 (s, 4, $-OCH_2-$) and 1.7 (m, 14).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.59; H, 9.89.

***trans*-Bicyclo[5.2.0]non-2-en-4-one Ethylene Ketal (40).**—To a solution of 9.73 g (0.0535 mol) of **39** in 45 ml of anhydrous ether at room temperature was slowly added 8.85 g (0.055 mol) of bromine. After addition was complete, a previously prepared solution of monosodium ethyleneglycolate in ethylene glycol (30 ml, 0.075 mol of base) was added with vigorous stirring. The resulting heterogeneous mixture was poured into water and extracted with additional portions of ether. The combined organic layers were dried and evaporated. The residue was dissolved in 80 ml of dry dimethyl sulfoxide at room temperature and 13.5 g (0.12 mol) of potassium *tert*-butoxide was added in small portions. The mixture was stirred for 2 hr at room temperature, poured into saturated sodium chloride solution, and extracted with ether. The organic phase was dried and the solvent was removed. Vacuum distillation of the residue gave 7.70 g (80%) of **40**, bp 58–68° (0.35 mm). Vpc analysis indicated that this material was greater than 98% pure: $\delta_{TMS}^{CCl_4}$ 5.63 (center of ABX, 2, J_{AB} = 2.2, J_{BX} = 2.8 Hz, olefinic), 3.88 (s, 4, $-OCH_2-$), 2.7 (m, 1, H_1), and 1.8 (br m, 9).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.47; H, 9.19.

***trans*-Bicyclo[5.2.0]-*cis*-non-2-en-4-one (41).**—A mixture of 7.70 g of **40** and 50 ml of 3% sulfuric acid was stirred at room temperature for 1 hr. The mixture was extracted with ether and the combined extracts were washed with sodium bicarbonate and sodium chloride solutions. The dried solution was distilled at atmospheric pressure to remove solvent, and then under reduced pressure to give 5.34 g (91%) of **41**: bp 77–79° (2.7 mm); $\delta_{TMS}^{CCl_4}$ 6.85 (center of A portion of ABX pattern, 1, J_{AB} = 11, J_{AX} = 2 Hz, H_2), 5.79 (d of q, B portion of ABX with further coupling, probably across the carbonyl, 1, H_3), 1.4–3.4 (br m, 12). The semicarbazone derivative melted at 187.5–191.0° (from ethanol).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.29; H, 8.91.

Hydrogenation of 41.—A 73-mg sample of **41** dissolved in 5 ml of ethyl acetate was hydrogenated at atmospheric pressure over 20 mg of 10% palladium on carbon. The mixture was filtered through Celite and concentrated under a stream of nitrogen. Saturated ketone **28** was isolated by preparative vpc (column D, 110°) and had ir and nmr spectra identical with those of a sample previously prepared.

4-Methylene-*trans*-bicyclo[5.2.0]non-2-ene (42).—To 5.90 g (16.5 mmol) of methyltriphenylphosphonium bromide in 60 ml of anhydrous ether was added under nitrogen 10.3 ml of 1.6 *N* *n*-butyllithium in hexane. After this solution was stirred for 45 min, 1.10 g (8.1 mmol) of **41** dissolved in 5 ml of ether was added. The mixture was refluxed for 12 hr, quenched with water, and extracted with additional ether. The dried ether extracts were evaporated and the residue was triturated with pentane. The filtered solution was distilled at atmospheric pressure and then under vacuum to give 638 mg of **42**, bp 72–80° (15 mm). Vpc analysis indicated that this material was 98–99% pure: $\lambda_{max}^{isooctane}$ 235 nm (ϵ 14,900), and 275 (1030); $\delta_{TMS}^{CCl_4}$ 5.77 (AB with further splitting, 2, H_2 and H_3), 4.70 (br s, 2, methylene protons), and 1.0–3.1 (br m, 10).

Anal. Calcd for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.57; H, 10.58.

Pyrolysis of 41.—Ketone **41** (344 mg) was pyrolyzed in the apparatus already described at 500° (10–15 mm). A total of 306 mg of condensate was collected in the cold trap. By vpc analysis (column F at 118°), this material was found to consist of a mixture of **43** (15)%, **44** (18%), starting ketone **41** (50%), and **45** (14%), with several additional minor products totaling 3%. Isolated 3,5-cycloheptadienone (**43**) (29 mg), 2,4-cycloheptadienone (**44**) (33 mg), and **45** (38 mg) were identified by their nmr spectra and by comparison with the authentic samples prepared below.

Unambiguous Synthesis of 43 and 44.—3,5-Cycloheptadienone (**43**) was obtained by lithium aluminum hydride reduction of tropone according to the literature procedure.[27] Purified **43** (53.5 mg) was pyrolyzed in the flow system at 390° (10 mm).[28] A quantitative mass balance was realized. Vpc analysis column F, 80°) indicated the presence of only two components in a ratio of *ca.* 50:50. The first component to be eluted from the column was **43**, while the second was the fully conjugated isomer **44**, identical with the sample obtained from pyrolysis of **41**.

Pyrolysis of 42.—Pyrolysis of 97.6 mg of **42** was carried out as before at 500° (25 mm). There was collected 73.2 mg of liquid that was analyzed by vpc and found to consist of **46** (73)%, **47** (18%), and 9% of several minor components. The mixture was separated by preparative vpc (column E, 65°). Triene **46** proved to be unstable and polymerized on standing: $\lambda_{max}^{isooctane}$ 283 nm (ϵ 16,000), 275 (sh, 15,000), and 299 (11,000); $\delta_{TMS}^{CCl_4}$ 5.5–6.3 (m, 4, olefinic), 4.7–5.0 (br d with further splitting, 2, methylene protons), and 2.1–2.7 (m, 4, allylics); calcd *m/e* 106.0782, observed 106.0783. Compound **47** was identified by synthesis as described below.

Alternate Preparation of 46. Wittig Reaction of 43 and 44.—To 4.63 g of methyltriphenylphosphonium bromide in 50 ml of anhydrous ether was added under a nitrogen atmosphere 8.1 ml of 1.6 *N* *n*-butyllithium in hexane. After this solution was stirred for 30 min, 700 mg of a 50:50 mixture of **43** and **44** dissolved in 5 ml of dry ether was added, and the mixture was refluxed overnight. At the conclusion of the reflux period, the mixture was quenched with water and extracted with ether. The ether solution was dried and carefully evaporated at atmospheric pressure. The residue was triturated with pentane to precipitate residual phosphorous compounds, and after filtration the pentane solution was evaporated and the residue was analyzed by vpc (column B, 65°). The major component (102 mg, 66% of the volatile material) was identical with **46** isolated from the pyrolysis. Also obtained was unreacted 3,5-cycloheptadienone (20%). In a control experiment carried out as above on 502 mg of pure **43**,

there was isolated a mixture consisting of 78% unreacted **43** and six minor products.

Synthesis of Authentic 47. A. Diels–Alder Reaction of Tropone and Maleic Anhydride.—This reaction was carried out as described[31] with the modification that unreacted maleic anhydride in the product was removed by sublimation at 80–90° (12–15 mm) until the nmr spectrum no longer showed the maleic anhydride singlet (88.5% yield). Hydrogenation and hydrolysis to **93** were carried out as previously outlined.[31]

B. Bicyclo[3.2.2]non-6-en-2-one (51).—To 55 ml of pyridine through which oxygen had been bubbled for 15 min was added 5.0 g (0.0221 mol) of diacid **50** and 14.7 g (0.0332 mol) of lead tetraacetate. The flask was immersed in a preheated oil bath at 68–73° for a period of 10 min. Gas evolution began shortly after immersion. At the conclusion of this time, the mixture was cooled in ice water, poured into cold, dilute (3 *M*) nitric acid, and extracted with ether. The combined organic extracts were washed with sodium bicarbonate solution, dried, and concentrated under reduced pressure to leave 1.72 g of crude yellow-brown semisolid. This material was sublimed at 60° (25 mm) to give 1.18 g (39%) of **51**, mp 87.5–88.5° (lit.[30] mp 89–90.8°). This compound is very volatile and will sublime at atmospheric pressure and room temperature: $\delta_{TMS}^{CDCl_3}$ 5.95–6.6 (m, 2), 3.06 (br m, 1), 2.6–2.9 (m, 3), 1.6–2.1 (br m, 6).

C. 2-Methylenebicyclo[3.2.2]non-6-ene (47).—To 3.17 g (8.8 mmol) of methyltriphenylphosphonium bromide in 50 ml of dry ether was added under a nitrogen atmosphere 7 ml (9.1 mmol) of 1.3 *N* *n*-butyllithium in hexane. After this solution was stirred for 15 min at room temperature, 0.600 g (4.4 mmol) of **51** dissolved in 3 ml of dry ether was added *via* a syringe. After refluxing for 13 hr the mixture was quenched with water and extracted with pentane. The combined pentane extracts were washed, dried, and filtered, and the solvent was evaporated at atmospheric pressure. The residue was vacuum transferred and the volatile material was found to contain greater than 95% of **47** by vpc analysis (column G at 118°): $\delta_{TMS}^{CDCl_3}$ 5.9–6.3 (m, 2, H_6, H_7), 4.57 (m, 2, methylene protons), 2.97 (br m, 1, H_1), 2.2–2.7 (m, 3), and 1.3–1.7 (m, 6, protons on C_4, C_8, C_9); calcd *m/e* for $C_{10}H_{14}$ 134.1095, observed 134.1092.

Anal. Calcd for $C_{10}H_{14}$. C, 89.49; H, 10.51. Found: C, 89.65; H, 10.57.

***cis*-Bicyclo[5.2.0]nonan-4-one (53) and 2-Methyl-*cis*-bicyclo[4.2.0]octan-3-one (54).**—To 0.452 mol of diborane (calcd as BH_2) (418 ml, 1.08 *M* in tetrahydrofuran) was added at 0° under a nitrogen atmosphere 39.1 g (0.465 mol) of 2,3-dimethyl-2-butene.[35] After stirring for 1.5 hr, the solution was transferred *via* syringe to one of two 500-ml addition funnels attached to a 2-l. three-necked flask also fitted with a magnetic stirrer and nitrogen inlet. The other addition funnel was charged with 48.5 g (0.45 mol) of *cis*-1,2-divinylcyclobutane[33] (90% pure, containing 4% butadiene, 4% 4-vinylcyclohexene). Sufficient dry tetrahydrofuran was added to the hydrocarbon to bring the two addition funnels to the same volume, and the two solutions were added simultaneously over a 5-hr period at 20–25° to 50 ml of dry tetrahydrofuran. The solution was cooled briefly to 0° and transferred rapidly under nitrogen pressure to a metal autoclave liver containing 16.5 g (0.92 mol) of distilled water. After the autoclave was sealed and flushed with carbon monoxide, the bomb was charged with *ca.* 900 psi of carbon monoxide and heated slowly over a period of 2 hr to 65°. Heating was discontinued and the mixture was allowed to cool slowly to room temperature overnight. The contents of the bomb were transferred to a flask, concentrated to about 100 ml under reduced pressure, and treated with 150 ml of 3 *N* sodium acetate solution. Hydrogen peroxide (150 ml, 30%) was added at such a rate to maintain the temperature at 30–45°. After addition was complete, the temperature was maintained for 1 hr at 50–60°. This cooled mixture was diluted with water and extracted with ether. After a crude distillation, the material boiling between 40° (3.0 mm) and 105° (0.3 mm) was combined with another run (0.124-mol scale) and redistilled. There was obtained 23.54 g (22%) of a 75:25 mixture of **53** and **54**, greater than 95% pure by vpc (column G at 140°), bp 65–80° (3.0 mm). Isolated **53** was identical with a sample prepared by the literature method.[26] **54** had $\delta_{TMS}^{CDCl_3}$ 3.0–1.3 (m, 11) and 2.1–1.8 (two overlapping d, J = 6.5 Hz, 3, methyls).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.98; H, 10.22.

***cis*-Bicyclo[5.2.0]nonan-4-one Ethylene Ketal (55).**—A mixture of 7.32 g (0.053 mol) of ketones **53** and **54** (*ca.* 65% of **53**), 6.58 g (0.016 mol) of ethylene glycol, and 100 mg of *p*-toluenesulfonic acid monohydrate was refluxed with stirring for 2 hr in 70 ml of benzene under a Dean–Stark trap. The mixture was cooled, diluted with water, and extracted with ether. The combined organic extracts were washed with saturated sodium bicarbonate and sodium chloride solutions and dried. The solvent was removed *in vacuo* and the residue was distilled, bp 69–80° (1.3 mm), yield 8.71 g (90%). Even on simple distillation with a short-path apparatus the latter fractions were enriched in **55**. **55** had $\delta_{TMS}^{CCl_4}$ 3.86 (s, 4, $-OCH_2-$) and 1.1–2.8 (br m, 14).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.44; H, 9.86.

***cis*-Bicyclo[5.2.0]non-2-en-4-one Ethylene Ketal (56).**—To 5.0 g (0.0274 mol) of somewhat impure **55** in 50 ml of dry ether was added dropwise at room temperature 4.65 g (0.0290 mol) of bromine. When all of the bromine had been consumed, a previously prepared solution of monosodium ethyleneglycolate (prepared from 1.27 g of sodium and 25 ml of ethylene glycol) was added with stirring. Water was added, the ether layer was separated, the aqueous phase was extracted several times with ether, and the combined organic extracts were dried and concentrated under reduced pressure. The last traces of solvent were removed *in vacuo* and the residue, without purification, was dissolved in 80 ml of dry dimethyl sulfoxide. To this solution was added 6.45 g (0.0575 mol) of potassium *tert*-butoxide with slight cooling. After stirring for 2 hr at room temperature, the dark mixture was poured into cold water and extracted four times with pentane. The combined pentane layers were washed with water and saturated sodium chloride solution, dried, and concentrated under reduced pressure. The residue was separated by distillation into two fractions. The first, bp 87–105° (1.3 mm), consisted of 3.05 g (62%) of unsaturated ketals (mostly **56**) and the second, boiling above 111° (1.3 mm), contained 1.21 g of unreacted bromo ketal. An analytical sample of **56** was prepared by preparative vpc (column F, 143°): $\delta_{TMS}^{CCl_4}$ 5.40 (br s, 2, olefinic), 3.84 (s, 4, $-OCH_2-$), and 1.0–3.0 (br, 10).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.19; H, 9.07.

***cis*-Bicyclo[5.2.0]non-2-en-4-one (45).**—A mixture of 3.05 g (0.017 mol) of unsaturated ketals in 1 ml of ether was stirred with 20 ml of 3% sulfuric acid for 3.5 hr at room temperature. At the conclusion of this time, the mixture was extracted four times with ether and the combined extracts were washed with water, sodium bicarbonate solution, and saturated salt solution. The dried solution was concentrated under reduced pressure to give 2.30 g of crude ketones. This material was distilled to remove a small amount of material with a very long vpc retention time, bp 62–75° (1.2 mm). The distillate was found by vpc analysis to be a mixture of about 50% of **45** and 50% of three other compounds which were not characterized. Pure **45** was obtained by preparative vpc on column H at 150°: $\delta_{TMS}^{CDCl_3}$ d of d (A portion of ABX, peak centers at 6.31 and 6.11, $J_{1,2}$ = 3.5, $J_{2,3}$ = 12.5 Hz, 1, H_2), d of t centered at 5.82 and 5.62 (1, H_3), 3.3 (br m, 1, H_1), and 1.4–3.0 (m, 9).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 78.98; H, 8.89.

Recycling of Unreacted Bromoketal. Bicyclo[5.2.0]non-1-en-4-one Ethylene Ketal (57).—To 0.75 g (2.9 mmol) of the recovered bromo ketal in 15 ml of dry dimethyl sulfoxide was added 0.64 g (5.8 mmol) of potassium *tert*-butoxide. After stirring for 17 hr at room temperature, the mixture was poured into water and extracted with pentane. The combined pentane extracts were washed with sodium chloride solution, dried, and evaporated to give 0.46 g (88%) of pale yellow oil identified by nmr analysis as **57**. The sample was purified by molecular distillation (0.36 g recovered), and vpc analysis (column F at 150°) indicated that this material was greater than 85% of a single component. An analytical sample was obtained by preparative vpc on the same column: $\delta_{TMS}^{CDCl_3}$ 5.2 (m, 1, olefinic), 3.92 (s, 4, $-OCH_2-$), and 1.0–3.3 (br m, 11).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.44; H, 8.99.

Hydrogenation of Bicyclo[5.2.0]non-1-en-4-one Ethylene Ketal (57).—Using the procedure previously employed, 30 mg of **57** was hydrogenated in 4 ml of ethyl acetate over 12 mg of 10% palladium on carbon. There was obtained 19 mg of saturated cis ketal **55** that was identical with material previously synthesized.

Hydrolysis of Ketal 57. Bicyclo[5.2.0]non-1-en-4-one (58).—A mixture of 0.30 g of **57** dissolved in ether (1 ml) and 15 ml of 3% sulfuric acid was stirred at room temperature for 4 hr. After an

ether extraction followed by washes of water and saturated sodium bicarbonate solution, the organic layer was dried and the solvent was removed under reduced pressure to give 0.18 g (80%) of **58**, $\delta_{TMS}^{CDCl_3}$ 5.2 (m, 1, olefinic) and 1.1–3.5 (br m, 11).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.07; H, 8.81.

Hydrogenation of Bicyclo[5.2.0]non-1-en-4-one (58).—Ketone **58** (8 mg) was hydrogenated in 3 ml of ethyl acetate over 12 mg of 10% palladium on carbon. After filtration of the catalyst and concentration of the solution, preparative vpc (column E at 150°) yielded 6 mg of **53**, whose identity was confirmed by an infrared spectrum. There was a minor impurity (*ca.* 5%) that was too limited in quantity for identification.

Acid Equilibration of 45 and 58.—Ketone **58** (25 mg) and 1 mg of *p*-toluenesulfonic acid monohydrate were dissolved in 3 ml of benzene. This solution was heated to reflux and progress of the reaction was followed by periodic examination of aliquots by gas chromatography (column F). After 1 hr, the peaks due to **45** and **58** were of approximately equal size. After several hours the relative areas did not change and integration of the peak areas indicated a 43:57 mixture of **58** and **45**.

4-Methylene-*cis*-bicyclo[5.2.0]non-2-ene (59).—To 6.30 g (17.6 mmol) of methyltriphenylphosphonium bromide in about 60 ml of anhydrous ether was added under nitrogen 13.5 ml of 1.3 *N* *n*-butyllithium in pentane (0.018 mol). After this solution was stirred for 15 min at room temperature, ketone **45** (1.20 g of a mixture 50% in **45**, 8.8 mmol) dissolved in 5 ml of dry ether was added *via* syringe. After being refluxed overnight, the reaction mixture was quenched with water and extracted with pentane. The combined pentane extracts were dried and the solvent was removed by distillation at atmospheric pressure. The residue was vacuum transferred from nonvolatile phosphorous compounds and shown by vpc (column F at 115°) to consist of two major and two minor components; the first component eluted (possibly still a mixture) was not identified but was clearly not the desired compound by nmr analysis; the second component was the desired **59**, and the third and fourth components were small amounts of unreacted ketones **58** and **45**. **59** had $\delta_{TMS}^{CDCl_3}$ 5.91 (d with further coupling, 1, H_3, A portion of ABX, $J_{2,3}$ = 12.5 Hz), 5.35 (d of d, B portion of ABX, $J_{2,3}$ – 12.5, $J_{1,2}$ = 4.3 Hz, H_2), 4.82 (br s, 2, methylene protons), 3.2 (br m, 1, H_1), and 1.2–2.9 (m, 9) (double irradiation of H_1 (341 Hz) on a Jeolco 100-MHz nmr instrument collapsed H_2 and H_3 to a clean AB quartet); calcd *m/e* 134.1095, observed *m/e* 134.1096.

Anal. Calcd for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.14; H, 10.53

Pyrolysis of *cis*-Bicyclo[5.2.0]non-2-en-4-one (45).—Pyrolysis was carried out as before, giving the results summarized in Table VI. 2,4- and 3,5-Cycloheptadienones (**44** and **43**) were identified by their infrared spectra. The order of elution from column F (140°) was **43**, **44**, **51**, and **45**. Bicyclo[3.2.2]non-6-en-2-one (**51**) displayed ir and nmr spectra identical with those of the authentic material prepared above.

Photoisomerization of 51. *cis*-3a,4,5,7a-Tetrahydro-1-indanone (60).—An analytical run was performed by photolyzing a 1% ether solution of **60** and cyclododecane in a Pyrex test tube attached to a Pyrex immersion well which housed a 200-W Hanovia lamp. Aliquots were removed at various intervals and analyzed by vpc. Starting material slowly disappeared and was replaced by one major component (84%), a second less predominant product (13%), and two very minor substances which remain unidentified. The major product was characterized as ketone **60** and the minor as aldehyde **61**.

A preparative run was carried out by photolyzing 480 mg of **51** in 25 ml of dry ether (purged with nitrogen) for 43 hr. At the end of this time, the mixture was concentrated under reduced pressure and the products were isolated by preparative vpc isolation from column H at 150°. **60** had $\delta_{TMS}^{CDCl_3}$ 5.65–5.90 (m, 2, olefinic) and 1.2–2.9 (10 H).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 78.98; H, 8.88.

61 had $\delta_{TMS}^{CDCl_3}$ 9.84 (t, J = 1.5 Hz, 1, –CHO), 5.5–6.1 (m, 4, olefinic), 1.4–2.7 (br m, 7); $\lambda_{max}^{cyclohexane}$ 260 mm (ε 5000); calcd *m/e* 136.0888, observed 136.0889. The 2,4-dinitrophenylhydrazone melted at 84–86.5° (from ethanol). The lack of sufficient material precluded elemental analysis.

Hydrogenation of 60 to *cis*-Perhydroindanone (62).—A sample of **60** (21 mg) in 5 ml of dry ether was hydrogenated over 25 mg of 10% palladium on carbon for 2 hr. The catalyst was filtered through Celite and the filtrate was concentrated in a stream of dry nitrogen. Vpc analysis on column H at 150° indicated that the product was greater than 95% pure. A sample collected from the vpc had an infrared spectrum identical with that of authentic *cis*-perhydroindanone (**62**).[44]

Isomerization of 60.—A pure sample of **60** was injected into a 12 ft × 0.25 in. vpc column packed with 10% QF-1 on 60/80 mesh Chromosorb G at 165–170° and was collected. The infrared spectrum of the material which was eluted last was identical with that of authentic **63**. On the second pass through the vpc column, approximately 50% conversion to **63** was achieved. When the temperature of the column was lowered to 145°, no isomerization of **60** was noted.

Chlorination–Dehydrochlorination of *cis*-Perhydro-1-indanone (62).—To 2.00 g (0.0145 mol) of **62**[44] in 10 ml of carbon tetrachloride at 0–15° was added dropwise 2.35 g (0.0174 mol) of sulfuryl chloride dissolved in 5 ml of CCl_4 over a period of 30–45 min. The mixture was stirred for an additional 1.5 hr, at which time water was added and the layers were separated. The organic layer was washed with saturated sodium bicarbonate and saturated sodium chloride solutions, and dried, and the solvent was distilled through a short column at reduced pressure. The residue (2.18 g) was dissolved in 30 ml of dry tetrahydrofuran and 1.87 g (0.0151 mol) of 1,5-diazabicyclo[4.3.0]non-5-ene was added. The mixture was refluxed for 5 hr, cooled, and diluted with pentane and water. The aqueous phase was extracted with pentane, and the combined organic extracts were dried and concentrated. The residue weighed 610 mg and it consisted of 2% minor components, 21% of the desired 3a,4,5,6-tetrahydro-1-indanone (**63**), and 77% of 4,5,6,7-tetrahydro-1-indanone (**65**). The mixture was separated by preparative vpc (column B at 142°) and furnished 62 mg of **63** and 243 mg of **65**. **63** had ν_{max}^{neat} 1720 and 1650 cm^{-1}; $\delta_{TMS}^{CCl_4}$ 6.49 (m, 1, olefinic), 1.7–2.9 br m, 11); calcd *m/e* 136.0888, observed *m/e* 136.0889. **65** had ν_{max}^{neat} 1690 and 1640 cm^{-1}; $\delta_{TMS}^{CCl_4}$ 1.4–2.6 (br m); calcd *m/e* 136.0888, observed *m/e* 136.0889.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.19; H, 9.12.

Pyrolysis of 59.—A 36.1-mg sample of pure **59** was pyrolyzed at 540° as before and 33.9 mg of a mixture was collected. After preparative vpc separation on column F at 95°, the three individual components, **59** (4%), **46** (68%), and **47** (21%), were identified by their infrared spectra.

Control Pyrolysis of 60.—Ketone **60** (44.3 mg) was pyrolyzed at 490° (30 mm), and the resulting mixture was analyzed by vpc (column I at 140°). Starting material represented 90% of the mixture (20.8 mg was isolated and identified by its infrared spectrum), and **63** was the largest other component (5%, 1.1 mg isolated), identified by its infrared spectrum. A similar control pyrolysis at 555° (25 mm) of 21.9 mg of **60** gave a mixture consisting of **62** starting material (3.6 mg isolated) and 11% of **63** (0.9 mg isolated). In both cases, the remainder of the material was distributed among no less than light minor components.

Preparative Scale Pyrolysis of 47.—Pure **47** (71.5 mg) was pyrolyzed in the flow apparatus at 555° (30 mm) under a slow stream of nitrogen carrier gas. Vpc analysis of the condensate indicated that 10% of the mixture was **46** and 85% consisted of unreacted **47**; there was also produced in a combined yield of 5% a mixture of five minor components. After preparative vpc (column G at 115°), 4.3 mg of **46** was collected and identified by its nmr spectrum; 47.9 mg of unreacted **47** was also collected for an overall mass balance of 75%.

Acknowledgment.—Partial financial support of this research has been provided by the Army Research Office (Durham).

Registry No.—**1a**, 24217-77-4; **1b**, 24217-81-0; **3a**, 24217-80-9; **3b**, 24217-82-1; **5**, 40954-22-1; **6**, 34956-68-8; **11**, 40954-24-3; **12**, 40954-25-4; **13**, 40954-26-5; **14**, 3721-30-6; **15**, 41021-31-2; **16**, 40954-28-7; **24**, 10095-80-4; **25**, 40954-30-1; **25** semicarbazone, 40954-31-2; **26**, 40954-32-3; **27**, 40954-33-4; **28**, 40954-34-5; **29**, 3513-11-9; **30**, 40954-37-8; **31**, 19744-63-9; **38**, 40954-

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38-9; **39**, 40954-39-0; **40**, 40954-40-3; **41**, 40954-41-4; **41** semicarbazone, 40954-42-5; **42**, 40954-43-6; **43**, 1121-65-9; **44**, 1901-34-4; **45**, 40954-46-9; **46**, 40954-47-0; **47**, 40954-48-1; **50**, 40954-49-2; **51**, 934-62-3; **52**, 16177-46-1; **53**, 40954-52-7; **54**, 40954-53-8; **55**, 40954-54-9; **56**, 40954-55-0; **57**, 40954-56-1; **58**, 40954-57-2; **59**, 40954-58-3; **60**, 40954-59-4; **61**, 40954-60-7; **61** 2,4-DNPH, 40954-61-8; **62**, 2826-65-5; **63**, 40954-63-0; **65**, 22118-00-9.

The Synthesis of an Analog of Camptothecin by a General Method

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Received May 1, 1973

The introduction of the α-hydroxybutyrate chain on the 4 position of β-picoline *via* the 4-lithio derivative gave **7**. The oxidation of the 3-methyl substituent required for lactone formation between the substituents on the 3 and 4 positions of **7** to give **14** could only be accomplished after introducing a chloro group adjacent to the ring nitrogen. The quaternization of **2** and the hydrolysis of the aryl-α-chloro substituent completed the synthesis of the camptothecin analog **16**.

The discovery was made that the alkaloid camptothecin (**1**) possessed a high activity against several mouse lymphocytic leukemias[2] and inhibited the growth of solid tumors as well. The isolation of the 10-hydroxy- and 10-methoxycamptothecin as minor alkaloids from *Camptotheca acuminata* provided compounds with activity against leukemia, L1210.[3] The limited availability of the natural material provided an impetus for the synthesis of camptothecin and led to several successful preparations during a 1-year period.[4] The toxicity observed on continued administration of camptothecin led to an increased interest in the synthesis of close structural analogs as a possible means of obtaining compounds which retained the desirable anticancer effects but with reduced chronic toxicity. This article reports a general method for the synthesis of such compounds using an analog with the A and B rings carbocyclic and a seco ring C to illustrate the method.

The antineoplastic activity of camptothecin has been shown to be associated with the pyridone and lactone systems of the D and E rings.[2] Simple D and E ring analogs having methyl substituents on the pyridone ring at the 6 position[4c] or 1 position[4f,g] have been reported and the former was reported to have 0.01 times the activity of camptothecin as a cytotoxic agent. The synthetic methods used for these analogs were not readily applicable for the preparation of a variety of N-substituted derivatives which might be converted to pentacyclic analogs. The synthetic scheme utilized in this study provided a logical approach to any aromatic pentacyclic analog as well as natural camptothecin.

The crucial intermediate in this synthesis was the pyrido-δ-lactone **2**. β-Picoline *N*-oxide[5] was nitrated following the procedure of Taylor and Crovetti to give the 4-nitro derivative **3**, which was converted by acetyl bromide[6] or hydrobromic acid[7] to 84 or 81% of 4-bromo-β-picoline 1-oxide (**4**), respectively. Attempts to cause the displacement of the nitro group by bromine and reduction of the *N*-oxide in the same reaction with phosphorus tribromide[7] gave a mixture of **5** and 4-nitro-β-picoline (**6**). A more satisfactory route to **5** was by the two-step conversion from **3** using Raney nickel catalyst to remove the *N*-oxide function from **4** following a procedure described for a related reaction.[8] This reaction gave 83% yields of **5**, isolated as the hydrobromide, with no complication of nucleophilic displacement of the 4-bromo group as was observed when phosphorus trichloride was used for the reduction.

Alkylation of 4-nitro-β-picoline 1-oxide (**3**) or 4-bromo-β-picoline 1-oxide (**4**) by nucleophilic displacement of the 4 substituent by a carbanion proved unsuccessful. Thus the sodium salts of ethyl cyanoacetate and diethyl ethylmalonate in several solvents failed to give reaction. Spectroscopic evidence for a very small yield from the reaction of the sodium salt of diethyl malonate and 4-bromo-β-picoline 1-oxide (**4**) was obtained. The yield could not be improved by the application of more vigorous reaction conditions, so the introduction of the 4 side chain by this approach was abandoned.

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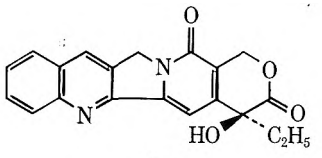
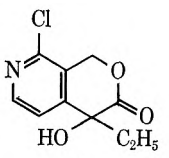


1



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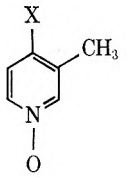
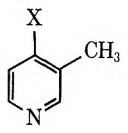
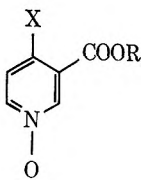


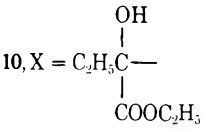
3, X = NO_2
4, X = Br



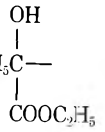
5, X = Br, HCl
6, X = NO_2



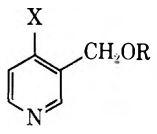
8a, X = NO_2; R = H
b, X = Br; R = H
c, X = CH_3O; R = CH_3
d, X = Cl; R = CH_3
e, X = Cl; R = H



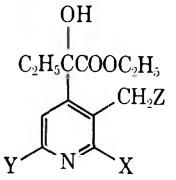
10, X = $C_2H_5C(OH)(COOC_2H_5)$—



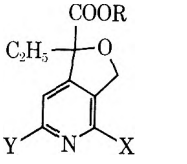
7, X = $C_2H_5C(OH)(COOC_2H_5)$—



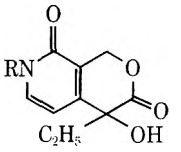
9a, X = Cl; R = H(HBr)
b, X = I; R = H(HBr)



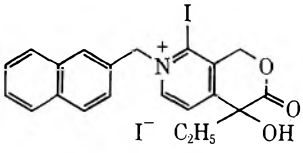
11a, X = Cl; Y = H; Z = Br
b, X = H; Y = Cl; Z = Br
13a, X = Cl; Y = H; Z = OAc
b, X = H; Y = Cl; Z = OAc



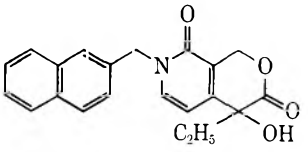
12a, X = Cl; Y = H; R = H
b, X = H; Y = Cl; R = H



14, R = H



15



16

The reported conversion of 4-bromopyridines to Grignard reagents was difficult;[9] however, the 4-lithio derivatives were reported to be formed by metal–halogen exchange and to undergo reaction with ketones successfully.[7,9] The reaction of 4-lithio-3-methylpyridine, from the reaction of **5** with *n*-butyllithium, with ethyl α-ketobutyrate gave a 52% yield of ethyl 2-hydroxy-2-(3′-methyl-4′-pyridyl)butyrate (**7**) which could be isolated in two crystalline forms, mp 72–73 and 108–110°. The solution spectra of the two forms were identical; however, the infrared spectra as mulls showed small but definite differences.

All attempts to brominate or oxidize the 3-methyl substituent of **7** to close the lactone ring failed.[10] The conversion of 4-nitronicotinic acid 1-oxide (**8a**) to 4-halo-3-hydroxymethylpyridines (**9**) could be accomplished; however, attempts to protect the hydroxyl group and form the 4-lithio derivative failed. Thus the introduction of the 4 side chain after the oxidation of the 3 substituent did not prove successful.

The discovery that the steric and electronic effects of a 2-chloro substituent permitted bromination of β-methyl quinolines and pyridines with *N*-bromosuccinimide[10] suggested a method of circumventing the difficulty in closing the lactone to form **2**. The conversion of **7** to the *N*-oxide **10** with *m*-chloroperoxybenzoic acid was easily accomplished and reaction of **10** with phosphorus oxychloride gave a mixture of 2- and 6-chloro derivatives which readily underwent benzylic bromination to form a mixture of **11a** and **11b** in 80% yield from **7**.

The treatment of the mixture of **11a** and **11b** with base in water or DMSO gave a product which clearly was a carboxylic acid, based on its solubility in base and conversion to a methyl ester in methanolic hydrogen chloride. The spectral data suggested that intramolecular cyclization had occurred with ether formation to give **12**, followed by saponification of the ester. The proton magnetic resonance spectrum of the methyl ester of **12** showed it to be the 2-chloro derivative only, for the aromatic hydrogens gave an AB quartet and there was no evidence of a mixture from the other signals as well.

Since the cyclization to form the ether was so rapid with strong base, it was evident that displacement of the benzylic bromide by a weakly basic oxygen nucleophile would be required prior to saponification of the ester. The mixture of **11a** and **11b** was therefore treated with potassium acetate in acetic acid to form the mixture of acetates **13a** and **13b**. Hydrolysis of the acetate mixture of **13a** and **13b** in methanolic potassium hydroxide and acidification gave 7-chloropyrido[5,4-*c*]-2-oxo-3-ethyl-3-hydroxy-3,6-dihydropyran (**2**) in 23% yield from the *N*-oxide **10**. No product could be isolated which arose from the 6-chloro series (**11b** and **13b**). Possibly the less hindered 6-chloro substituent underwent nucleophilic displacement to give the pyridone which was lost in the isolation of **2**.

The 2-chloro group of **2** was inert to nucleophilic displacement in acidic or basic media. The pyridone **14** was formed by photochemical nucleophilic substitution.[11]

The formation of quaternary salts of **2** was very difficult. Heating **2** with methyl iodide, benzyl bromide, or 2-bromo-3-bromomethylquinoline failed to give any salt. The addition of sodium iodide to the reaction mixture of **2** and 2-bromomethylnaphthalene with no solvent gave a quantitative yield of the 2-napthylmethyl iodide salt of 7-iodopyrido-[5,4-*c*]-2-oxo-3-ethyl-3-hydroxy-3,6-dihydropyran (**15**). The salt **15** on standing in dimethyl sulfoxide[12,13] was cleanly converted to the pyridone **16** in quantitative yield.

The reactions provide a general procedure for the preparation of pyridone analogs of camptothecin. This route is currently being explored as a method of preparing other such compounds.

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(12) R. E. Lyle and M. J. Kane, *J. Org. Chem.*, in press.

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Experimental Section

Preparation of 4-Bromo-β-picoline Hydrochloride (5).—A solution of 4-bromo-β-picoline *N*-oxide[7] (4) (20.0 g, 0.106 mol) in 200 ml of methanol was reduced with hydrogen (1 atm over water) over about 3 g of W-2 Raney nickel[14] until hydrogen uptake ceased (about 3 hr). A total of 2.5 l. of hydrogen (about 93% of the theoretical amount) was absorbed. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to remove most of the methanol. The residual liquid was diluted with 600 ml of dry ether, and the mixture was filtered. The filtrate was treated with gaseous HCl, and the hydrochloride was collected by filtration, washed with several portions of ether, and then dried in a vacuum desiccator to give 18.4 g (83%) of 4-bromo-β-picoline hydrochloride (5), mp 177–179°. An analytical sample was prepared by two recrystallizations of the salt from acetonitrile–ether to give pure 5, mp 178–179°.

Anal. Calcd for C_6H_7BrClN: C, 34.53; H, 3.35; N, 6.71. Found: C, 34.38; H, 3.15; N, 6.59.

Preparation of Ethyl 2-Hydroxy-2-(3′-methyl-4′-pyridyl)butyrate (7). A. From 4-Bromo-β-Picoline (5).—A solution of freshly distilled 4-bromo-β-picoline (16.2 g, 94.2 mmol), prepared from the hydrochloride 5 in 125 ml of dry ether was cooled to −50° in an addition funnel surrounded by Dry Ice. This solution was added dropwise over 0.5 hr to a stirred solution of 100 mmol of *n*-butyllithium in 66 ml of hexane and 100 ml of ether which was cooled in a Dry Ice–2-propanol bath. The reaction mixture was stirred for an additional 0.25 hr and then 14.0 g (108 mmol) of ethyl α-ketobutyrate[15] in 100 ml of ether was added over 10 min. The reaction mixture was stirred for an additional 0.3 hr and then allowed to warm to −30°. To this mixture was added dropwise 40 ml of 10% HCl. After warming to 0°, the layers were separated and the organic layer was extracted four times with 30-ml portions of 10% HCl. The combined acidic extracts were extracted with three 50-ml portions of ether, and the acidic solution was then basified with solid sodium carbonate. The basic solution was extracted with three 200-ml portions of ether, and the extract was dried (K_2CO_3) and concentrated under reduced pressure to give an orange oil which partially crystallized on standing for 18 hr in an ether–pentane solution in the refrigerator. The solid was separated by filtration and washed with cold pentane to give 6.5 g (31%) of crude 7, mp 70–73°. An analytical sample, mp 70–71°, was prepared by vacuum sublimation.

Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.57; H, 7.62; N, 6.28. Found: C, 64.54; H, 7.79; N, 6.28.

B. From 4-Bromo-β-picoline Hydrochloride (5).—4-Bromo-β-picoline hydrochloride (5) (13.5 g, 64.5 mmol) was basified with a cold slurry of concentrated K_2CO_3 solution and the basic solution was extracted with 350 ml of ether in several portions. The extract was dried (K_2CO_3) and concentrated to a volume of 125 ml. Under a positive pressure of nitrogen, this ethereal solution was added over 0.5 hr to a vigorously stirred solution of 78 mmol of *n*-butyllithium in 50 ml of hexane and 80 ml of ether kept in a Dry Ice–2-propanol bath. The reaction mixture was stirred for an additional 0.25 hr and then 10.0 g (76.9 mmol) of ethyl α-ketobutyrate in 75 ml of ether was added over 5 min. The reaction was worked up as in A to give 7.5 g (52%) of the second allotropic form of 7, mp 102–104°, which gave pmr and ir spectra in solution identical with those of the form which melted at 70–71°.

Preparation of 4-Bromonicotinic Acid *N*-Oxide (8b).—4-Nitronicotinic acid *N*-oxide (8a)[16] (70.0 g, 0.381 mol) was added slowly to 285 ml of cold acetyl bromide. The mixture was then heated under reflux for 1 hr. The reaction mixture was cooled and the solid product was collected by filtration and washed with cold acetone and cold water. The solid was dried in a vacuum desiccator to give 62.7 g (76%) of 8b, mp 155° dec. An analytical sample was prepared by two recrystallizations of the solid from water to give 8b, mp 167° dec.

Anal. Calcd for $C_6H_4NBrO_3$: C, 33.02; H, 1.84; N, 6.42. Found: C, 32.86; H, 1.82; N, 6.35.

Preparation of Methyl 4-Methoxynicotinate *N*-Oxide (8c).—Following the method of Taylor and Crovetti,[17] a mixture of 6.00 g (32.6 mmol) of 4-nitronicotinic acid *N*-oxide (8a) and 120 ml of methanol was cooled to 0° and treated with gaseous HCl for 10 min. After 5 min, solution was achieved. The reaction was heated under reflux for 2 hr, and the solvent was removed by distillation under reduced pressure. Water was added to the residue and potassium carbonate was added. Extraction into chloroform, drying, and concentration gave an oil which crystallized with ether to give 3.4 g (57%) of 8c, mp 101–104°,[18] picrate mp 144–145.5° (lit.[17] mp 146–147°). The esterification of 8a with methanol using hydrogen bromide as catalyst also gave 8c, mp 118–121°.

Preparation of Methyl 4-Chloronicotinate *N*-Oxide (8d). A. From 4-Bromonicotinic Acid *N*-Oxide (8b).—A mixture of 29.0 g (0.133 mol) of 4-bromonicotinic acid *N*-oxide (8b) and 150 ml of purified thionyl chloride was heated under reflux for 0.75 hr. Excess thionyl chloride was removed by distillation under reduced pressure, the residue was dissolved in 150 ml of cold methanol, and after 1 hr at room temperature the excess was removed by evaporation. The residue was dissolved in 100 ml of chloroform, and the solution was added dropwise to a slurry of saturated K_2CO_3 solution (100 ml) and chloroform (100 ml) at −5°. The layers were separated and the aqueous layer was filtered. The filter cake was washed with three 100-ml portions of chloroform which were then used to extract the aqueous solution. The combined extracts were dried (K_2CO_3) and concentrated under reduced pressure to give a light yellow solid which was triturated thoroughly with pentane and then dried in a vacuum desiccator to give 15.5 g (62%) of the methyl ester 8d, mp 105–106°.[19] An analytical sample, mp 105.5–106.5°, was prepared by two recrystallizations from benzene.

Anal. Calcd for $C_7H_6NClO_3$: C, 44.80; H, 3.20; N, 7.46. Found: C, 44.64; H, 2.97; N, 7.60.

Preparation of Methyl 4-Chloronicotinate *N*-Oxide (8d). B. From 4-Chloronicotinic Acid *N*-Oxide (8e).—4-Chloronicotinic acid *N*-oxide (8e) (40.0 g, 0.231 mol) was added to 200 ml of thionyl chloride and the mixture was heated under reflux for 0.5 hr. The excess thionyl chloride was removed by evaporation under reduced pressure and residual solid was dissolved in 150 ml of cold methanol and stirred in an ice bath for 0.25 hr. Ether (300 ml) was added, and the white solid which precipitated was collected by filtration. A solution of the solid in water was neutralized with potassium carbonate and worked up as in A to give 36.0 g (83%) of 8d, mp 116–117° dec, picrate mp 118–119° (methanol).

Preparation of Methyl 4-Chloronicotinate Hydrobromide.—A stirred solution of methyl 4-chloronicotinate *N*-oxide (8d) (20.0 g, 0.107 mol) in 200 ml of methanol was reduced with hydrogen (1 atm) over W-2 Raney nickel (21 g added in approximately three equal portions over 2.75 hr). The total uptake of hydrogen during this period was about 2 l. (90% of the theoretical amount). The product was isolated as in the preparation of 5 to give 24.1 g (89%) of the ester hydrobromide, mp 144–145° dec. An analytical sample, mp 138.5–140° dec, was prepared by recrystallization from acetone.

Anal. Calcd for $C_7H_7NBrClO_2$: C, 33.27; H, 2.77; N, 5.54. Found: C, 32.74; H, 2.70; N, 5.24.

Preparation of 4-Chloro-3-hydroxymethylpyridine Hydrobromide (9a).—Methyl 4-chloronicotinate hydrobromide (11.5 g, 45.7 mmol) was converted to the base with cold K_2CO_3 solution. To a solution in 75 ml of dry ether was added 38.8 mmol of $LiAlH_4$ in 65 ml of ether over 0.3 hr while cooling. Stirring was continued for 1 hr and then the reaction mixture was hydrolyzed by the successive dropwise addition of 1.5 ml of water, 1.5 ml of 15% NaOH, and then 4.5 ml of water and filtered. The filter cake was washed with ether, and the combined ether washings were dried and concentrated to give a light yellow solid which was taken up in ether and treated with anhydrous hydrogen bromide. The white product was collected by filtration, washed with ether, and dried in a vacuum desiccator to give 7.60 g (74%) of 9a, mp 160.5–161°.

Anal. Calcd for $C_6H_7BrClNO$: C, 32.07; H, 3.11; N, 6.23. Found: C, 32.16; H, 2.88; N, 5.94.

Preparation of 4-Iodo-3-hydroxymethylpyridine Hydrobromide (9b).—A mixture of 4-chloro-3-hydroxymethylpyridine hydrobromide (9a) (3.00 g, 13.4 mmol), sodium iodide (18 g), and methyl ethyl ketone (150 ml) was heated under reflux in an oil

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(18) The melting point of this compound was erroneously reported as 141–143° in ref 17.

(19) The melting point was reported to be 84° in ref 17.

bath for 23 hr. Treatment with water, base, and 40% sodium bisulfite solution gave the base of **9b** which was taken up in acetone and saturated with HBr. Ether (50 ml) was added to the mixture, and the salt was collected and washed with several portions of ether to give 2.79 g (66%) of **9b**, mp 161–162°.

Anal. Calcd for C_6H_7BrINO: C, 22.78; H, 2.21; N, 4.43. Found: C, 23.56; H, 2.14; N, 4.32.

Preparation of Ethyl 2-Hydroxy-2-(3′-methyl-4′pyridyl)butyrate *N*-Oxide (10).—A solution of ethyl 2-hydroxy-2-(3′-methyl-4′-pyridyl)butyrate (7) (1.00 g, 4.48 mmol) and 85% *m*-chloroperbenzoic acid (1.36 g, 6.72 mmol) in 40 ml of chloroform was allowed to stand at room temperature for 3 hr. The solution was poured into water and made basic with solid potassium carbonate. This solution was extracted with four 40-ml portions of chloroform, and the extract was dried (K_2CO_3) and concentrated under reduced pressure to give 940 mg (88%) of **10**, mp 172–173°. An analytical sample, mp 175.5–176°, was prepared from two recrystallizations from acetone.

Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.30; H, 7.12; N, 5.86. Found: C, 60.58; H, 7.19; N, 5.99.

Preparation of Ethyl 2-Hydroxy-2-[2′(6′)-chloro-3′-bromomethyl-4′-pyridyl]butyrate (11a and 11b).—A solution of *N*-oxide **10** (860 mg, 3.50 mmol) in 10 ml of $POCl_3$ was heated under reflux in an oil bath for 0.5 hr. After cooling the solution was poured over crushed ice and neutralized with solid K_2CO_3. The basic solution was extracted with four 50-ml portions of ether, and the extract was dried (K_2CO_3) and concentrated under reduced pressure to give 880 mg (95%) of the α-chloro derivative which was brominated without further purification.

A mixture of the chloropyridines (770 mg, 2.95 mmol), NBS (670 mg, 3.76 mmol), a catalytic amount of dibenzoyl peroxide, and 15 ml of carbon tetrachloride (stored over 4-A molecular sieves) was heated under reflux by means of a 100-W bulb for 3.5 hr. An additional 350 mg (1.97 mmol) of NBS was added and the heating was continued for 2.5 hr. The mixture was cooled and filtered. The filter cake was washed with several portions of CCl_4, and the filtrate was concentrated under reduced pressure to give 920 mg (92%) of **11a** and **11b** which was used directly.

Hydrolysis of 11a and 11b with Potassium Hydroxide in Aqueous DMSO.—To the bromomethylpyridines **11** (1.25 g, 3.70 mmol) from above was added a 2 *N* solution of KOH in 1:1 DMSO–H_2O and the solution was allowed to stand at ambient temperature for 3 hr. Water and hydrochloric acid were added and the solution was extracted with several portions of chloroform. The extract was dried (Na_2SO_4) and concentrated under reduced pressure to give 500 mg (59%) of **12** as a yellow oil: ir (neat) 3500–2500 and 1720 cm^{-1}; pmr ($CDCl_3$) δ 0.92 (t), 1.20 (m), 2.15 (m), 5.27 (s), 7.53 (d, 4.5 Hz), 8.49 (d, 4.5 Hz), and 11.6 (s).

Preparation of 7-Chloropyrido[5,4-*c*]-2-oxo-3-ethyl-3-hydroxy-3,6-dihydropyran (2).—A solution of crude brominated pyridines **11** (920 mg, 2.85 mmol) from above and 1.40 g of potassium acetate in 10 ml of acetic acid was heated at 110° in an oil bath for 10 hr. The mixture was then poured into ice water and basified with solid $NaHCO_3$. The solution was extracted with three 50-ml portions of chloroform and the extract was dried (K_2CO_3) and concentrated under reduced pressure to give 660 mg (73%) of the acetate **13** as a brown oil. The oil was dissolved in a 1 *N* solution of KOH in 5 ml of methanol and 5 ml of water, and the solution was heated under reflux for 2.5 hr. The solution was then poured into 40 ml of water and chilled in an ice bath. Concentrated HCl was added until the solution was acidic; and after stirring for 0.25 hr, solid $NaHCO_3$ was added until the solution had been neutralized. Extraction with three portions of chloroform gave, after drying (K_2CO_3) and concentration under reduced pressure, an oil which solidified to give 94.3 mg (20%) of **2**, mp 95–105°. In another set of experiments, **2** was isolated in about 35% yield from **13** and in 23% yield from the *N*-oxide **10**. An analytical sample of **2**, mp 116–119°, was prepared by three vacuum sublimations.

Anal. Calcd for $C_{10}H_{10}ClNO_3$: C, 52.74; H, 4.39; N, 6.15. Found: C, 52.53; H, 4.52; N, 6.36.

Photolysis of 7-Chloropyrido[5,4-*c*]-2-oxo-3-ethyl-3-hydroxy-3,6-dihydropyran (2).—A dilute solution of **2** in concentrated hydrochloric acid was irradiated for 16 min with a 450-W Hanovia lamp using a Vycor filter. The ultraviolet absorption of **2** at the start showed absorption at 263 nm with a shoulder at 270 nm. After the irradiation the solution gave maximum absorption at 295, 264 (sh), and 255 nm, corresponding to the absorption of the pyridone **14**.

Preparation of the 2-Naphthylmethyl Quaternary Salt of 2.—To 200 mg (0.88 mmol) of 7-chloropyrido[5,4-*c*]-2-oxo-3-ethyl-3-hydroxy-3,6-dihydropyran (**2**) and 200 mg (0.88 mmol) of 2-bromomethylnaphthalene was added 256 mg (1.7 mmol) of sodium iodide. The mixture was heated under nitrogen in an oil bath. When the oil bath reached 125° a solid had formed and heating was discontinued. Ethyl acetate was added and the insoluble solid was separated by filtration and washed with water and ether. After drying the solid a quantitative yield of the quaternary salt **15**, mp 182.5–184°, was obtained.

Anal. Calcd for $C_{21}H_{19}I_2NO_3$: C, 42.95; H, 3.26; N, 2.38. Found: C, 42.54; H, 3.25; N, 2.48.

Preparation of the Pyridone 16 from the Salt 15.—A solution of the quaternary salt **15** in dimethyl sulfoxide was allowed to stand for 2 weeks at room temperature. The solution was poured into water and ether was added. The solid which precipitated was removed by filtration and washed with water and ether. After drying, the solid represented a quantitative yield of the pyridone **16**, mp 187–189°.

Anal. Calcd for $C_{21}H_{19}NO_4 \cdot H_2O$: C, 68.65; H, 5.22; N, 3.81. Found: C, 68.73; H, 5.29; N, 4.11.

Acknowledgment.—The authors wish to express appreciation to the National Cancer Institute of the National Institutes of Health for partial support of this research by grant CA-12149-01 and -02. The *n*-butyllithium used in this research was generously suppled by Foote Mineral Co. by Dr. O. F. Beumel.

Registry No.—**2**, 40899-34-1; **4**, 10168-58-8; **5**, 10168-00-0; **5** hydrochloride, 40899-37-4; **7**, 40899-38-5; **8a**, 1078-05-3; **8b**, 40899-40-9; **8c**, 40899-41-0; **8c** picrate, 40899-42-1; **8d**, 40899-43-2; **8d** picrate, 40899-44-3; **8e**, 1074-93-7; **9a**, 40899-46-5; **9b**, 40899-47-6; **10**, 40899-48-7; **11a**, 40899-49-8; **11b**, 40899-50-1; **12a**, 40899-51-2; **15**, 40899-52-3; **16**, 40899-53-4; methyl 4-chloronicotinate hydrobromide, 40899-54-5.

Chromatographic Adsorption. VI. Isomer Distribution and Mechanism of Formation of the Methyl Glycosides of D-Glucose and D-Galactose by the Fischer Method

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Received January 4, 1973

The formation of the four methyl D-glucosides from D-glucose and the four methyl D-galactosides from D-galactose, using a strongly acidic ion-exchange resin as catalyst, was followed by gas–liquid partition chromatography of their trimethylsilyl ethers. The final equilibrium mixtures in refluxing methanol contained approximately 73% methyl α-D-glucopyranoside and 27% methyl β-D-glucopyranoside and 60% methyl α-D-galactopyranoside, 17% methyl β-D-galactopyranoside, 5% methyl α-D-galactofuranoside, and 18% methyl β-D-galactofuranoside, respectively. Reaction mechanisms for the acid-catalyzed alcoholysis of hexoses, 6-deoxyhexoses, and pentoses are proposed.

The previous paper in this series[1] reported the change of isomer distribution with time for the Fischer reaction of methanol with D-mannose and with L-arabinose using a cation-exchange resin as catalyst and liquid chromatography on a starch column as the analytical method. This analytical procedure failed to separate the reaction products of the Fischer reactions of D-glucose or D-galactose. It has since been reported[2] that a separation of the methyl D-glucosides has been effected by gas–liquid partition chromatography of their *O*-trimethylsilyl derivatives on a Carbowax 6000 column at 140°. Preliminary work in this laboratory with a 25 ft × 1/8 in. copper column packed with 10% Carbowax 6000 on acid-washed Chromosorb W (80–100 mesh) did yield five peaks, as reported, but the order of elution appeared to be slightly different from that reported; the column rapidly deteriorated after a sample or two had been run through, possibly due to attack of the silylation mixture upon the stationary phase at the temperature required, 170°. Several other columns were tried and the most successful was a high efficiency 50 ft × 1/8 in. stainless steel column furnished by Analabs, Inc., which contained 4.8% OV-17 on 80–100 mesh Anakron H. This column showed no deterioration at the required temperature of 205° but failed to separate the α- and β-D-glucopyranosides. Since these were the only components of the mixtures that were not resolved and since they differ markedly in their optical activity, a polarimetric measurement upon each sample withdrawn from the reaction mixture, in addition to the gas chromatographic analysis, allowed calculation of the mole per cent of each component present.

In the case of the methyl D-galactosides a partial separation by gas chromatography of their trimethylsilyl ethers has been reported[2] and a complete analysis by use of two different columns demonstrated. We have found it possible to effect a complete separation of the trimethylsilyl ethers of α- and β-D-galactose and the four methyl D-galactosides using a 26 ft × 1/8 in. copper column containing 9% OV-1 on Chromosorb W-HP (80–100 mesh).

Experimental Section

Materials.—D-Glucose and D-galactose were Pfanstiehl CP materials of specific rotations +52.5 and +80.2°, respectively. Methyl α-D-glucopyranoside, of specific rotation +159.5°, was obtained from Corn Products Refining Co; and methyl β-D-glucopyranoside, of specific rotation −33.8°, from Mann Research Labs. Methyl α-D-galactopyranoside and methyl β-D-galactopyranoside of specific rotations +190 and 0°, respectively, were obtained as recrystallized crystalline products from a Fischer reaction. The methanol was reagent grade and the strongly acidic ion-exchange resin was Dowex-50W (X-8) 50–100 mesh, equilibrated with methanol as described previously.[1] Pyridine was obtained from Reilly Tar and Chemical Corp., Indianapolis, Ind., and was dried over sodium hydroxide pellets. Trimethylchlorosilane, hexamethyldisilazane, *O*-trimethylsilyl α-D-glucose, *O*-trimethylsilyl β-D-glucose, and *O*-trimethylsilyl α-D-galactose were all obtained from Pierce Chemical Co., Rockford, Ill.

Methyl Glycoside Formation.—Fischer glycosidation of D-glucose and D-galactose was carried out essentially as described previously.[1] Complete solution of 50 g of glucose in 195 g of methanol occurred in 20–30 min and of galactose in about 15 min, and equilibrium was reached in about 12 hr for glucose and 24 hr for galactose. Aliquots (0.1 ml) of the 1-ml pyridine-quenched samples were vacuum evaporated several times with dry pyridine to remove the methanol and the trimethylsilyl ethers were formed by addition of 1 ml of dry pyridine, 0.2 ml of hexamethyldisilazane, and 0.1 ml of trimethylchlorosilane according to the method of Sweeley, *et al.*[3]

For the polarimetric measurements 7-ml samples were withdrawn. The resin was allowed to settle in a 60° bath and weighed aliquots containing a few milligrams of $NaHCO_3$ were evaporated under vacuum at 50°. The residue was made up to a volume of 25.75 ml and the optical rotation determined at 22° in a 4-dm tube using a sodium lamp. Polarimeter readings and sample weights, respectively, follow: for D-glucose 0.5 hr, 4.40°, 4.43 g; 1 hr, 5.30°, 4.40 g; 2 hr, 6.40°, 4.39 g; 4 hr, 9.90°, 4.42 g; 8 hr, 13.01°, 4.45 g; 12 hr, 15.85°, 4.45 g; 24 hr, 24.07°, 6.73 g; 48 hr, 19.59°, 5.42 g and for D-galactose 1 hr, −0.72°, 4.38 g.

Chromatography of the Trimethylsilyl Ether Derivatives.—A Hewlett-Packard Model 5750 gas chromatograph with a FID was used with either the previously mentioned 50 ft × 1/8 in. OV-17 column for D-glucose or the 26 ft × 1/8 in. OV-1 column for D-galactose reaction mixtures. A Perkin-Elmer printing integrator was used to determine peak areas from the OV-17 column and a planimeter for the areas of the peaks from the OV-1 column, as these were eluted on the trailing edge of the solvent peak. In the latter case vacuum evaporation of the silylated samples and addition of 1 ml of *n*-hexane produced level baselines and yielded the same peak areas as before this treatment. Sample injections varied from 0.5–5 μl and electrometer attenuations from $10^2/4$ to $10^3/1$. Prepurified nitrogen at 40 psi and 25 ml/min was used for the OV-17 column and 50 psi and 20 ml/min for the OV-1 column. Relative detector constants for the pure materials available were found to be 1.00 ± 0.02 and were therefore assumed to be 1.00 for all components of the silylated mixtures. Reproducibility of the reaction conditions was found to be within about ±2 for the mole per cent of each component of the mixtures.

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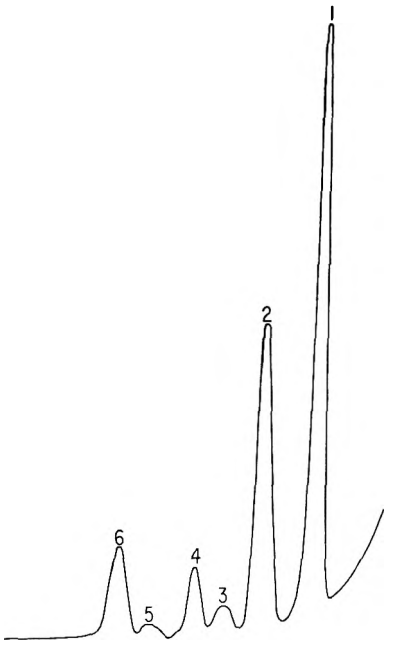


Figure 1.—Silylated 0.25-hr methyl D-galactoside reaction mixture chromatographed at 190° and 50 psi on a 26 ft × 1/8 in. copper column packed with 9% OV-1 on 80–100 mesh Chromosorb W-HP. Peak order and retention times (in min): 1, β-furanoside (35); 2, α-pyranoside (41); 3, β-pyranoside (46); 4, α-D-galactose (49): 5, α-furanoside (54); 6, β-D-galactose (58).

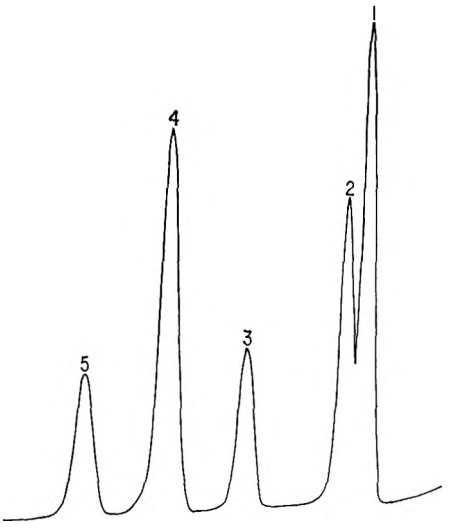


Figure 2.—Silylated 1-hr methyl D-glucoside reaction mixture chromatographed at 205° and 40 psi on a 50 ft × 1/8 in. stainless steel column packed with 4.8% OV-17 on 80–100 mesh Anakron H. Peak order and retention times (in min): 1, β-furanoside (46); 2, α-furanoside (49); 3, α-D-glucose (61); 4, α- and β-pyranosides (71); 5, β-D-glucose (82).

Discussion

Identification of Peaks in the Methyl D-Galactoside Mixtures.—Figure 1 shows the chromatogram produced by the 0.25-hr silylated methyl D-galactoside reaction sample. Peak identity for α- and β-D-galactose and methyl α- and β-D-galactopyranosides was established using authentic samples. The peaks produced by the two furanosides were distinguished by comparison of the observed molecular rotation of the reaction mixture at 1 hr, −900°, with that calculated assuming the first peak is β-furanoside and the fifth peak is α-furanoside, −500°. If the first peak is assumed to be α-furanoside and the fifth peak β-furanoside, then the calculated molecular rotation is +22,700, proving conclusively that the first peak must be β-furanoside and the fifth peak α-furanoside. The specific rotations used for these calculations[2] were +104, −113, +80, +192, and 0° for the α-furanoside, β-furanoside, D-galactose, α-pyranoside, and β-pyranoside, respectively.

Identification of Peaks in the Methyl D-Glucoside Mixtures.—Figure 2 shows the chromatogram produced by the 1-hr silylated methyl glucoside reaction sample. Peak identity for α- and β-D-glucose and methyl α- and β-D-glucopyranosides was established using authentic samples. Peaks produced by methyl α-D-glucofuranoside and methyl β-D-glucofuranoside were identified by comparison with a chromatogram of the same sample on Carbowax 6000, for which stationary phase the first and second peaks have been identified by Smirnyagin, Bishop, and Cooper[2] as methyl β-D-glucofuranoside and methyl α-D-glucofuranoside, respectively. Confirmation of this assignment comes from calculation of the molecular rotation of the reaction mixture at 0.5 hr as described below. The figure of 5640 is obtained, and, if the first peak is assumed to be β-furanoside and the second α-furanoside, a value of 11,700 is calculated for the molecular rotation of the unresolved α- and β-pyranosides. This yields figures of 8 and 9 mol %, respectively, for α- and β-pyranoside in the reaction mixture and a value of 0.9 for the ratio of α/β. If, on the other hand, the first peak is assumed to be α- and the second β-furanoside, a value of −3900 is obtained for the molecular rotation of the unresolved α- and β-pyranosides, which leads to values of 1 and 16 mol %, respectively, for α- and β-pyranoside and a value of 0.06 for the ratio of α/β. From the areas under peak 2 (α-pyranoside), peak 3 (β-pyranoside + α-D-glucose) and peak 4 (β-D-glucose) of the 0.25-hr sample chromatographed on the OV-1 column and the ratio of β- to α-D-glucose of 1.2 from the OV-17 column, the ratio of α-pyranoside/β-pyranoside may be calculated as 0.8. Since the α-pyranoside/β-pyranoside ratio increases as the reaction proceeds, it is evident that this ratio cannot have a value of 0.06 for the 0.5-hr sample; therefore the first peak must be β-furanoside and the second α-furanoside.

Calculation of Mole Percentages of the D-Glucopyranosides.—The mole per cent of α-pyranoside, $100 \cdot X_4 \cdot (R_1 - R_6)/(R_5 - R_6)$, and of β-pyranoside, $100 \cdot X_4 \cdot (R_5 - R_4)/(R_5 - R_6)$, was calculated from the observed polarimeter reading, a, of the given aliquot of weight, c, from the reaction mixture by means of the two relationships

$$R(\text{expt}) = (a \times 25.75 \times 180 \times 245)/(c \times 4 \times 50)$$

$$R_4 \times X_4 = \text{r(expt)} - X_1 \times R_1 - X_2 \times R_2 - X_3 \times R_3$$

where R represents molecular rotation and X mol fraction, obtained from the chromatogram, and 1 refers to α-furanoside (+118°), 2 to β-furanoside (−77°), 3 to D-glucose (+52.5°), 4 to the α- + β-pyranoside mixture, 5 to α-pyranoside (+158°) and 6 to β-pyranoside (−34°). The ratio of α/β glucopyranoside was also determined chromatographically in two cases using the OV-1 column. Retention times in minutes on this column at 200° follow: α- and β-furanosides (28), α-

pyranoside (38), α-D-glucose and β-pyranoside (42), and β-D-glucose (58).

Results.—Tables I and II show the variation with time of each component in the Fischer reactions of

TABLE I

MOLE PERCENTAGES DURING REACTION OF D-GALACTOSE

Time, hr	D-Galactose α	D-Galactose β	Furanosides α	Furanosides β	Pyranosides α	Pyranosides β
0[a]	32	68				
1/12	17	29		27	25	2
1/6	12	21	1	35	28	3
1/4	8	12	1	46	29	4
1/2	7	9	2	48	29	5
1	2	1	2	57	30	8
2	1	1	4	48	35	11
4	1		5	33	44	17
8			4	30	49	17
12			5	26	52	17
24			5	18	60	17
48			5	18	60	17

[a] After 0.5-hr reflux but before addition of ion-exchange resin.

TABLE II

MOLE PERCENTAGES DURING REACTION OF D-GLUCOSE

Time, hr	D-Glucose α	D-Glucose β	Furanosides α	Furanosides β	Pyranosides α	Pyranosides β
0[a]	46	54				
1/12	31	35	13	18	3	
1/6	26	29	16	25	4	
1/4	19	21	20	31	4	5[b]
1/2	14	16	23	30	8	9[c]
1	11	13	20	26	15	15[c]
2	8	10	12	18	28	24[c]
4	4	4	5	8	46	33[c]
8	1	2	2	3	61	31[c]
12		1		1	71	27[c]
24					73	27[c]
48					73	27[b]

[a] After 0.5-hr reflux but before addition of ion-exchange resin. [b] Calculated from the α/β ratio obtained from the OV-1 column. [c] Calculated from polarimetric measurements.

D-galactose and of D-glucose, respectively. The composition of the equilibrium mixture for the D-glucose reaction falls within the limits of the 73 ± 5% methyl α-D-glucopyranoside and 27 ± 5% methyl β-D-glucopyranoside found by Capon, *et al.*,[4] for the methanesulfonic acid catalyzed reaction at 35°. Also, reaction of L-arabinose and analysis of silylated aliquots on the OV-17 column yielded essentially the same curves as obtained previously[1] using liquid chromatography. A comparison of the data of Table I with the isomer distribution curves of the homomorphous L-arabinose[1] and of the data of Table II with the curves of the homomorphous D-xylose[5] shows the expected similarities in the latter case but marked differences in the former case, in which it should be noted that the α and β designations are interchanged since the sugar is in the L series.

Proposed Mechanism for Methyl Glycoside Formation.—A satisfactory mechanism for methyl glycoside formation must be capable of explaining (a) the ratio of furanosides to pyranosides initially formed, (b) the ratio of α- to β-furanoside and α- to β-pyranoside initially formed, and (c) the fact that the same final equilibrium mixture of principally pyranosides is formed from any one of the methyl glycosides if subjected to Fischer reaction conditions.[1,5] It is immediately apparent that a and b are a result of kinetic control of the reaction whereas c results from thermodynamic control. The latter requires that all steps in the mechanism be reversible. Schemes I and II show a proposed mechanism applied to methyl D-galactoside and to methyl D-glucoside formations, respectively. These sugars differ from each other in the configuration of the C_4 hydroxyl group only; so their marked difference in the initial ratio of furanosides to pyranosides and α to β isomers must be due to this alone. The intermediate in the equilibration of the α and β forms of the sugars before addition of the ion-exchange resin is formulated classically as the aldehydo form (**2**) of the sugar and after addition of the resin the formation of this intermediate would be expected to be accelerated by protonation of the ring oxygen to give cation **5** in each case. In these cases the intermediate cannot be the resonance stabilized monocyclic carboxonium ion (**13**), shown below in the schemes, which would be produced by protonation of the anomeric hydroxyl group and loss of water, since this intermediate would react with methanol to give an immediate and rapid formation of methyl pyranosides rather than the furanosides actually obtained in the case of D-glucose.

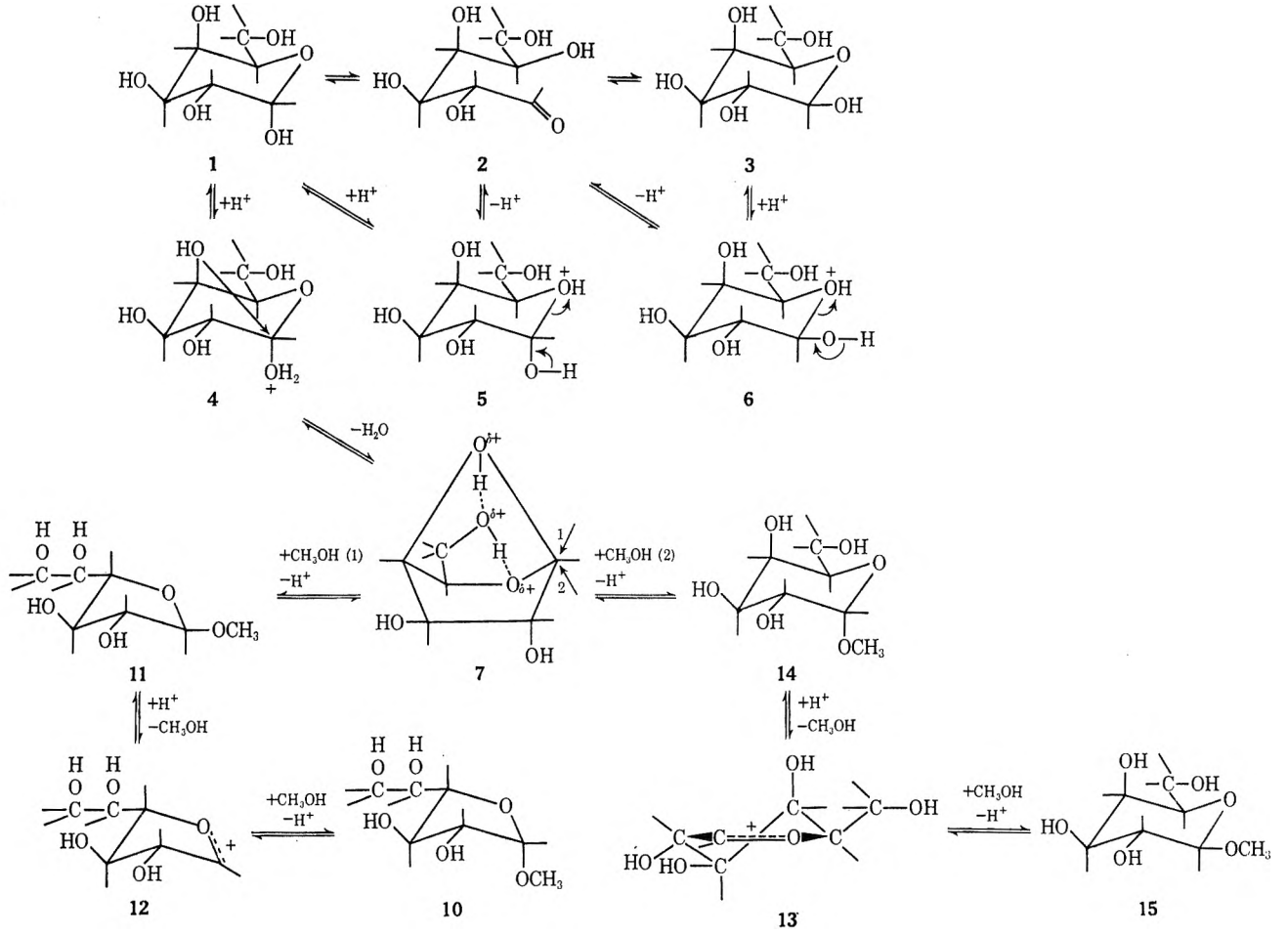
In the proposed mechanism for glycoside formation protonation of the anomeric hydroxyl group of α-D-galactose (**1**) in Scheme I or of β-D-glucose (**3**) in Scheme II is the first step. Water is then eliminated from the protonated form (**4**), in each case with anchimeric assistance from the C_4 hydroxyl group. In both cases a bicyclic cation (**7**) protonated on the C_4 ring oxygen is postulated.[4] In the case of D-galactose the C_6 hydroxyl group is in a position to hydrogen bond with the proton on the C_4 ring oxygen and at the same time form a hydrogen bond to the C_5 ring oxygen, thus producing a lower energy more stable cation in which the positive charge is distributed to three oxygen atoms. Attack of methanol upon this cation at the positions shown by the arrows 1 and 2 in Scheme I, followed by loss of a proton, would produce β-D-galactofuranoside (**11**) and α-D-galactopyranoside (**14**), respectively. The initial formation of β-furanoside and α-pyranoside in almost equal quantities suggests an equal distribution of positive charge on the C_4 and C_5 ring oxygen atoms. Assumption of this bicyclic cation stabilized by a double hydrogen bonding appears to explain the unusual isomer distribution found in the methyl D-galactoside formation at the 1/12-hr time. The 2% of β-D-galactopyranoside (**15**) may be accounted for by the anomerization of the α-pyranoside *via* the corresponding monocyclic carboxonium cation (**13**) proposed by other investigators.[5,6] If all steps in the mechanism are assumed reversible, the higher energy furanosides should gradually reform the bicyclic cation (**7**) and become converted into the lower energy pyranosides. In the case of methyl glucoside formation, shown in Scheme II, β-D-glucose (**3**) is protonated on the anomeric hydroxyl and this protonated form (**4**) loses water with anchimeric assistance from the C_4 hydroxyl. However, in this case the new oxygen

(4) B. Capon, G. W. Loveday, and W. G. Overend, *Chem. Ind. (London)*, 1537 (1962).

(5) C. T. Bishop and F. P. Cooper, *Can. J. Chem.*, **40**, 224 (1962).

(6) B. Capon, *Chem. Commun.*, **1**, 21 (1967).

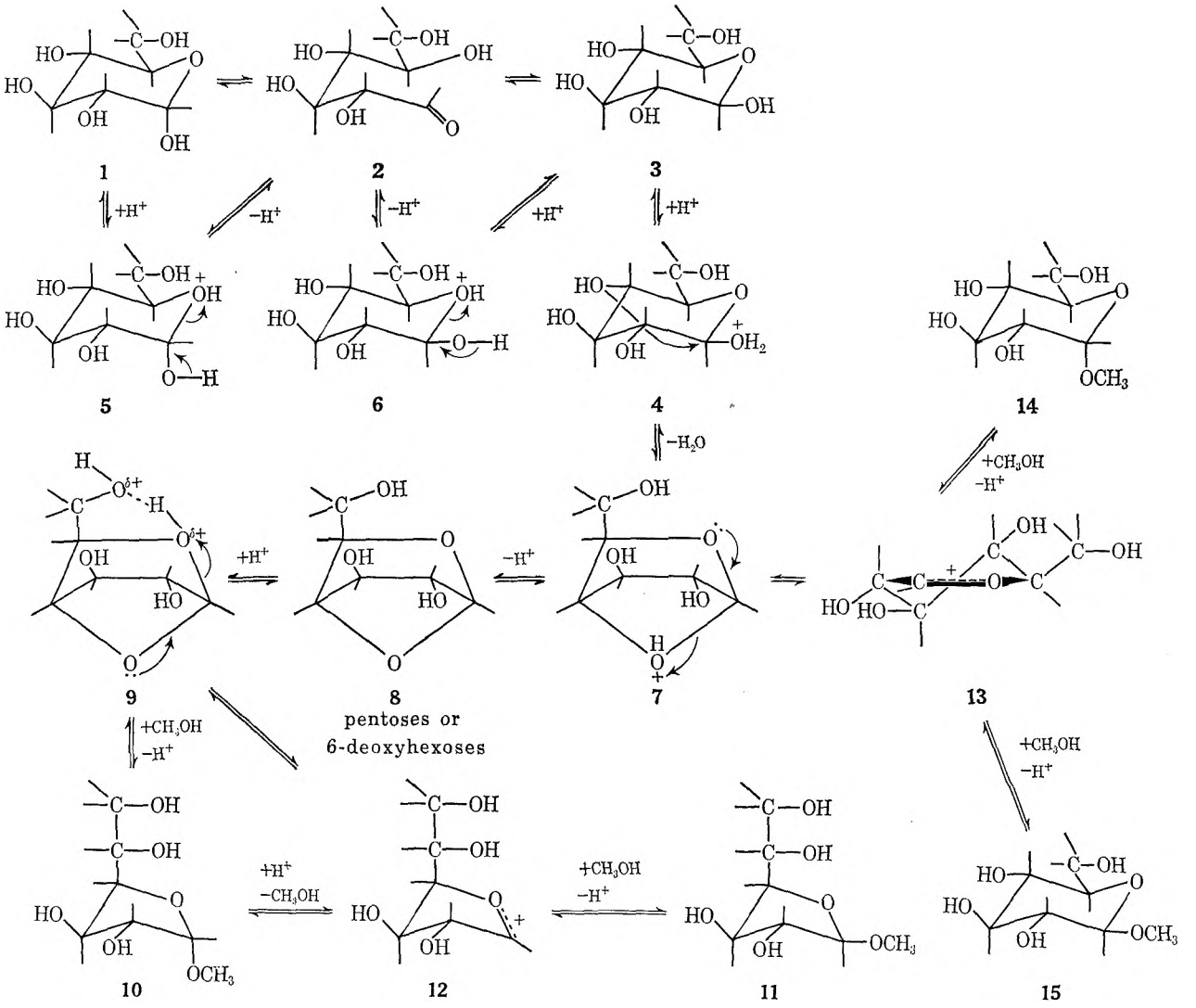
SCHEME I



bridge forms *below* the pyranose ring rather than *above* it so that the C_6 hydroxyl in the bicyclic cation (**7**) is not in a position to hydrogen bond and stabilize the protonated C_4 ring oxygen atom. A rapid equilibrium is assumed between this bicyclic cation (**7**) and the bicyclic cation protonated on the C_5 ring oxygen (**9**), which should be stabilized by hydrogen bonding with the C_6 hydroxyl. This equilibrium should favor the lower energy hydrogen-bonded bicyclic cation and thereby lead to a more rapid initial formation of furanosides than pyranosides. It is assumed that this stabilized bicyclic cation is attacked by methanol and forms α-D-glucofuranoside (**10**), which rapidly[4] equilibrates with β-D-glucofuranoside (**11**) *via* the monocyclic carboxonium cation (**12**). An alternative mechanism, probably the major one for pentoses and 6-deoxyhexoses, might be direct formation of the monocyclic carboxonium cation (**12**) by SN1 ring opening in the bicyclic cation (**9**). This appears less likely in the case of glucose since hydrogen bonding between the proton on the C_5 ring oxygen and the C_6 hydroxyl would reduce the positive charge on the ring oxygen and thereby reduce the tendency for opening of this ring. In the case of the formation of the glucopyranosides (**14** and **15**) from the unstabilized bicyclic cation (**7**), on the other hand, SN1 ring opening to form the monocyclic carboxonium cation (**13**) would be expected and must be assumed since otherwise the initial samples would show predominantly β-pyranoside (**15**) from attack by methanol on the bicyclic cation (**7**) followed by the much slower[4] β- to α-pyranoside anomerization. The very slightly faster rate of β-pyranoside (**15**) over α-pyranoside (**14**) formation during the first half hour of the reaction could be due to slightly greater blocking of attack by methanol on the monocyclic carboxonium cation (**13**) by the C_2 hydroxyl than by the C_6 hydroxyl group.

This proposed mechanism for acid-catalyzed alcoholysis of carbohydrates would be expected to have three modifications depending on whether the C_4 and C_5 hydroxyl groups of a hexose are of (1) the same configuration or (2) opposite configurations or whether (3) the C_6 hydroxyl group is absent as in the case of pentoses and 6-deoxyhexoses. The *first* type should resemble D-glucose in initial furanoside/pyranoside and α/β ratios. D-Mannose, for example, when subjected to the same conditions as D-glucose and D-galactose, has been found[1] after $^1/_8$ hr to yield a mixture having a furanoside/pyranoside ratio of approximately 4.0, an α/β furanoside ratio of about 1.9 and an α/β pyranoside ratio of about 3.5. These ratios are to be compared with corresponding ratios after $^1/_{12}$ hr for D-glucose of about 10, 0.7, and 0.7 and for D-galactose of about 1.0, 0.0, and 8.3. In comparison with D-glucose the smaller furanoside/pyranoside ratio for D-mannose may be explained by inductive electron withdrawal through the solvent by the C_2 hydroxyl, which has opposite configurations in the mannose and glucose bicyclic intermediates (**8**) in Scheme II. This would decrease the basicity of the C_5 ring oxygen and increase that of the C_4 ring oxygen in D-mannose, with a resulting decrease in the furanoside/pyranoside ratio. The

SCHEME II



larger α/β furanoside ratio for D-mannose is undoubtedly caused by the slower anomerization of the α-D-mannofuranoside first formed to its equilibrium value of about 1.0 than of the α-D-glucofuranoside (**10**) to its equilibrium value of about 0.7. The larger initial α/β pyranoside ratio for D-mannose is probably due to an increased rate of α-pyranoside (**14**) and a decreased rate of β-pyranoside (**15**) formation caused by inverting the configuration of the C_2 hydroxyl group in the monocyclic carboxonium cation (**13**). The *second* type should resemble D-galactose, with a much smaller furanoside/pyranoside ratio and widely divergent α/β furanoside and pyranoside ratios. In the *third* type the C_6 hydroxyl is absent and therefore cannot hydrogen bond and stabilize the bicyclic cation intermediate. The mechanism would be expected to resemble that shown for D-glucose (Scheme II) except that the CH_2OH group would be replaced by either H or CH_3, eliminating the possibility of its hydrogen bonding with either protonated ring oxygen atom. Protonation on the C_5 ring oxygen (**9**) should be favored since inductive withdrawal of electrons from it by the C_3 hydroxyl group should be less than from the nearer C_4 ring oxygen. This should lead to predominantly furanosides *via* SN1 ring opening to produce the *furanose* monocyclic carboxonium cation (**12**). The bicyclic cation protonated on the less basic C_4 ring oxygen (**7**) would lead to smaller amounts of pyranosides *via* the *pyranose* monocyclic carboxonium cation (**13**). The actual structure of the bicyclic cation (**7**) would depend on the configuration of the C_4 hydroxyl, resembling in one case the D-glucose (Scheme II) and in the other the D-galactose (Scheme I) bicyclic cation. Since neither of these cations would be stabilized by internal hydrogen bonding, the less stable rings resulting would be expected to open to monocyclic carboxonium cations (**12** and **13**) before reacting with methanol. For the reaction of L-arabinose[1] [Scheme I with CH_2OH replaced by H and the bicyclic cation (**7**), protonated on the C_4 ring oxygen, assumed in equilibrium with the corresponding form protonated on the C_5 ring oxygen] the ratio of furanosides/pyranosides at $^1/_8$ hr is about 10 and of α/β furanosides and also α/β pyranosides about 0.9. The furanoside/pyranoside ratio could be due to the greater expected basicity and protonation of the C_5 ring oxygen as compared to the C_4 ring oxygen of the bicyclic intermediate because of reduced electron withdrawal by the more distant C_3 hydroxyl group. The α/β furanoside ratio of almost unity would result from an expected almost equal rate of attack by methanol upon both sides of the monocyclic carboxonium cation (**12**) in the preferred E_3 conformation with all three ring substituents equatorial. The α/β pyranoside

ratio of near unity would be expected if some SN2 attack by methanol on the bicyclic cation (7) to produce α-pyranoside (14) offsets a slight decrease in rate of formation of this isomer because of blocking of attack upon one side of the monocyclic carboxonium ion (13) by the C_2 hydroxyl group.

Registry No.—D-Galactose, 59-23-4; methyl α-D-galactofuranoside, 3795-67-3; methyl β-D-galactofuranoside, 1824-93-7; methyl α-D-galactopyranoside, 3396-99-4; methyl β-D-galactopyranoside, 1824-94-8; D-glucose, 50-99-7; methyl-α-D-glucofuranoside, 1824-88-0; methyl β-D-glucofuranoside, 1824-89-1; methyl α-D-glucopyranoside, 97-30-3; methyl β-D-glucopyranoside, 709-50-2.

The Synthesis of 4-β-D-Ribofuranosyl-*as*-triazin-3(4*H*)-one 1-Oxide, a Potential Uridine Antagonist[1]

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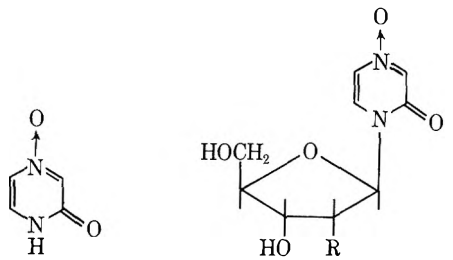
Received March 21, 1973

4-β-D-Ribofuranosyl-*as*-triazin-3(4*H*)-one 1-oxide (**8**), a structural analog of uridine, has been prepared by the reaction of 3-methoxy-*as*-triazine 1-oxide (**3**) with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**5**) followed by debenzoylation with $NaOCH_3$. Both proton and carbon-13 nmr were used to assign the site of nitrogen ribosylation, the first such reported application to a six-membered heterocyclic system. An unusual deoxygenation of the *N*-oxide function of 4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*as*-triazin-3(4*H*)-one 1-oxide (**6**) with ethanolic ammonia resulted in the formation of 4-β-D-ribofuranosyl-*as*-triazin-3(4*H*)-one (**10**). Reduction of the *as*-triazine ring of **6** was found to occur to yield 2,5-dihydro-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*as*-triazin-3(4*H*)-one (**11**). Small coupling constants for the anomeric protons of **6** and **8** were found to change to larger values on reduction of the aglycon portion of the molecule. pK_a measurements on *as*-triazin-3(4*H*)-one 1-oxide (**7**) and on the reduced product 2,5-dihydro-*as*-triazin-3(4*H*)-one (**15**) point out the unusual character of the *as*-triazin-3(4*H*)-one 1-oxide ring system.

Emimycin, an antibiotic isolated[2] from Streptomyces No. 2020-I, has been shown to be 2(1*H*)-pyrazinone 4-oxide (**1**).[3] The antibacterial activity of **1** is reversed by uracil, uridine, and 2′-deoxyuridine.[4] The syntheses of 1-β-D-ribofuranosylemimycin (**2**) and 1-β-D-2′-deoxyribofuranosylemimycin (**2a**) have recently been



1 2, R = OH 2a, R = H

reported.[5,6] The increased potency of **2a** over that of emimycin as a bacteriocidal agent illustrates the desirability of studying related nucleoside derivatives.

The present work describes the syntheses of *as*-triazin-3(4*H*)-one 1-oxide (**7**) (3-azaemimycin) and of the corresponding uridine analog 4-β-D-ribofuranosyl-*as*-triazin-3(4*H*)-one 1-oxide (**8**) (Scheme I). The synthesis of 3-methoxy-*as*-triazine 1-oxide (**3**) by oxidation of 3-methoxy-*as*-triazine (**4**) with perbenzoic acid has been reported in 15% yield.[7] Utilizing *m*-chloroperbenzoic acid[8] in refluxing benzene, the yield of **3** was increased to 30%. Treatment of **3** with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**5**) in acetonitrile yielded a single nucleoside product, 4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*as*-triazin-3(4*H*)-one 1-oxide (**6**) plus small amounts of another product which was identified as *as*-triazin-3(4*H*)-one 1-oxide (**7**) on the basis of pmr, mass spectra, and elemental analysis. The formation of **7** can be explained by the hydrolysis of 3-methoxy-*as*-triazine 1-oxide (**3**) by residual HBr and/or acetic acid, which are difficult to remove completely in the preparation of halogenose **5**. Addition of dilute methanolic HCl to an acetonitrile solution of **3** resulted in the formation of **7**.

Treatment of **6** with sodium methoxide removed the benzoyl blocking groups to give the desired uridine analog 4-β-D-ribofuranosyl-*as*-triazin-3(4*H*)-one 1-oxide (**8**). The assignment of the β-glycosidic configuration of **6** and **8** was based on the very small coupling constant of the anomeric proton observed in the pmr spectrum of **8** (*vide infra*).

Reductive removal of the *N*-oxide function was accomplished by hydrogenation of **8** in the presence of a 5% palladium-on-charcoal catalyst, but simultaneous reduction of the triazine ring was also observed. Unexpectedly, the formation of the nucleoside 4-β-D-ribofuranosyl-*as*-triazin-3(4*H*)-one (**10**) was found to occur upon treatment of the blocked nucleoside **6** with alcoholic ammonia. This deoxygenation of the *N*-oxide function of **6** with ethanolic ammonia at room temperature was indeed surprising, since only one analogous reaction could be found in the literature,[9] and in this example more vigorous conditions, heating in liquid NH_3 at 150°, resulted in the formation of 4,4′-dichloro-3,3′-dipicolyl from the corresponding di-*N*-oxide. Nevertheless, because both **6** and **8** were found to be completely stable even in refluxing EtOH, it

(1) This work was presented in part before the Division of Medicinal Chemistry at the 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 1972.

(2) M. Terao, K. Karasawa, N. Tanaka, H. Yonehara, and H. Umezawa, *J. Antibiot., Ser. A*, **13**, 401 (1960).

(3) M. Terao, *J. Antibiot., Ser. A*, **16**, 182 (1963).

(4) J. R. DeZeeuw and E. J. Tynan, *J. Antibiot., Ser. A*, **22**, 386 (1969).

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(6) P. T. Berkowitz, T. J. Bardos, and A. Bloch, *J. Med. Chem.*, **16**, 183 (1973).

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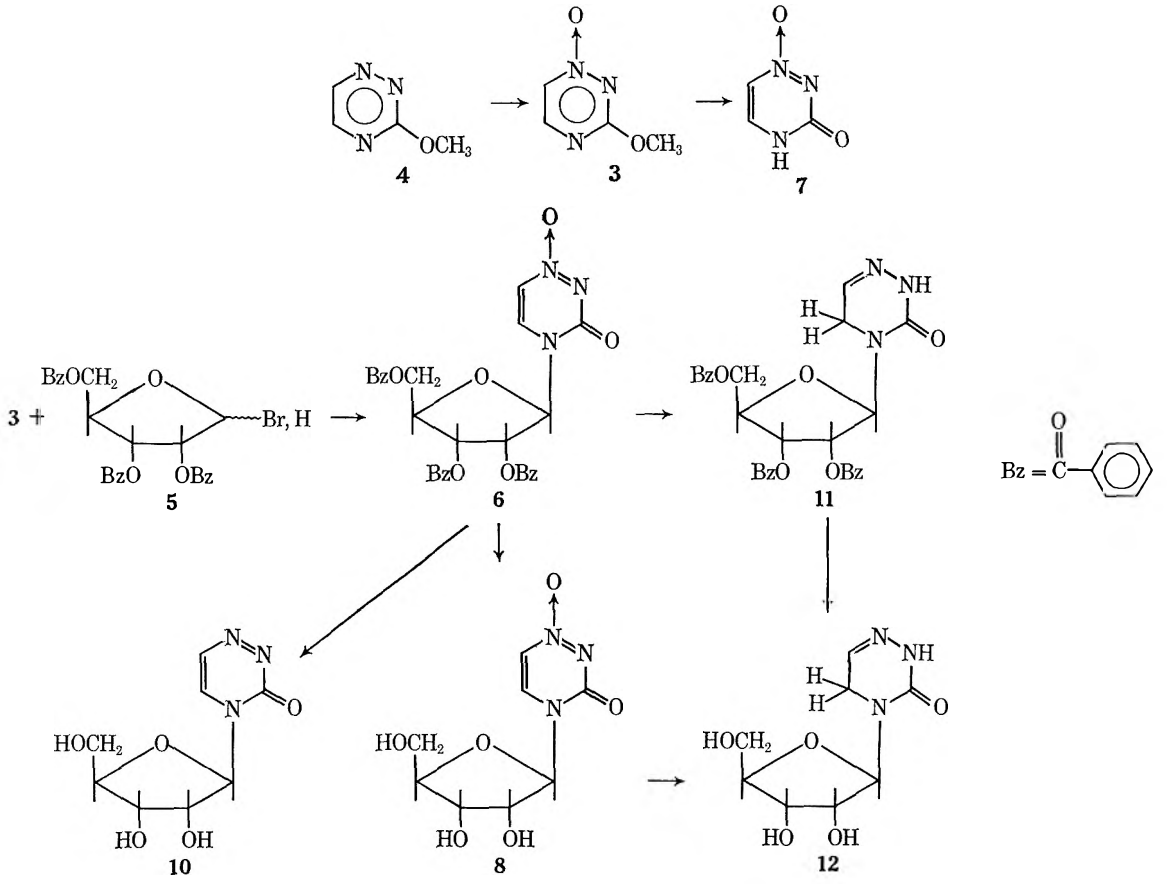
(8) (a) T. J. Della, M. J. Olsen, and G. B. Brown, *J. Org. Chem.*, **30**, 2766 (1965); (b) A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic *N*-Oxides," Academic Press, New York, N. Y., 1971, p 49.

(9) E. C. Taylor, A. J. Crovetti, and N. E. Boyer, *J. Amer. Chem. Soc.*, **79**, 3549 (1957).

SCHEME I



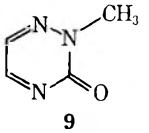
was established without doubt that this unusual deoxygenation was due to the effect of NH_3 rather than to the solvent EtOH applied in the above reaction.

TABLE I

UV SPECTRA OF 9 AND 10

	9	10
EtOH	λ_{max} 243 (ϵ 2608)	λ_{max} 225–226 (ϵ 6981)
	λ_{max} 309 (ϵ 655)	λ_{sh} 255 (ϵ 4936)
		λ_{sh} 346 (ϵ 2400)
pH 1	λ_{max} 243 (ϵ 3304)	λ_{max} 226–227 (ϵ 6487)
	λ_{max} 310 (ϵ 604)	λ_{sh} 225 (ϵ 4795)
		λ_{sh} 346 (ϵ 2120)
pH 11	λ_{max} 243 (ϵ 3022)	λ_{max} 234 (ϵ 6008)
	λ_{max} 310 (ϵ 353)	λ_{max} 347 (ϵ 2891)

The uv spectra of **10** (Table I) at various pH values were found to be substantially different from the uv spectra recorded for 2-methyl-*as*-triazin-3(2*H*)-one (**9**).[10] This eliminated position 2 as a site of glycosylation.



9

The first use of both proton and carbon-13 nmr to establish the glycosylation site has been reported by our laboratories in the case of 1-β-D-ribofuranosyl-1,2,4-triazoles.[11] The assignment was based on the use of the previously reported α and β substitution shifts observed in other heterocyclic systems when the neutral species is compared with the anionic form.[12-14] The use of both proton and carbon-13 nmr to confirm the site of ribosylation of the nucleosides **6** and **8** is the first reported instance of such a study for a six-membered heterocyclic ring system.

The nmr data are summarized in Table II. The proton assignments in the *as*-triazine 1-oxides were made assuming the same relative ordering of the H_5 and H_6 protons reported by Paudler and Chen[7] for 3-methoxy-*as*-triazine 1-oxide (**3**). The H_6 resonance was observed to occur at 1.54 ppm upfield from the H_5 resonance. Upon introduction of the ribose group the

TABLE II

^1H AND ^{13}C CHEMICAL SHIFTS OF *as*-TRIAZINE 1-OXIDES

	Pmr[a]		Cmr[b]			
Compd	H_5	H_6	C_3	C_5	C_6	CH_3
4	9.24	8.78	165.6	152.0	145.6	55.4
3	9.37	7.83	167.3	156.4	125.6	55.7
7	8.22	7.70	151.8	142.4	120.9	
8	8.78	7.80	153.4	138.6	120.9	
Anion of 7	8.18	7.52	164.9	152.2	118.9	

[a] Pmr spectra of 10% Me_2SO solutions were obtained on a 60-MHz Hitachi Perkin-Elmer R20A nmr spectrometer with a probe temperature of 34°. Chemical shifts are reported in parts per million downfield from internal DSS. [b] Cmr spectra of 40% Me_2SO solutions were obtained on a Bruker HX-90 nmr spectrometer operating at 22.62 MHz in the Fourier Transform Mode at a probe temperature of 35°. Chemical shifts are reported in parts per million downfield from internal TMS.

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H_6 resonance shifts downfield by 0.1 ppm, whereas the H_5 resonance exhibits a greater downfield shift of 0.56 ppm compared with **7**. This implies that the ribose is attached to the N-4, since otherwise the ribose group would exert a greater effect on H_6. Similar ribosylation effects on shifts of α hydrogens have been reported.[11,15]

The carbon-13 chemical shifts of 3-methoxy-*as*-triazine 1-oxide (**3**) and *as*-triazin-3(4*H*)-one 1-oxide (**7**) are also presented in Table II along with the values of the anion of **7** and 3-methoxy-*as*-triazine (**4**). The carbon-13 methyl resonance and the carbonyl resonance are readily identified, since they appear at high field and at low field, respectively, compared to the remainder of the resonance positions. However, the C_5 and C_6 resonances cannot be readily distinguished. A comparison of the chemical shift changes of the corresponding carbon-13 resonances in 3-methoxy-*as*-triazine (**4**) and their counterparts in the *N*-oxide **3** revealed that the resonance at 145.6 ppm from TMS exhibits an upfield shift of 20 ppm when the *N*-oxide is introduced in the 1 position and was therefore assigned to the C_6 resonance. Similar upfield shifts were observed for carbons adjacent to N-1 in adenosine 1-oxide *vs.* adenosine.[16] The remaining resonance at 152.0 ppm must be due to the C_5 resonance. The carbon-13 spectra of compounds **7** and **8** are assigned accordingly with the C_6 resonance appearing upfield from the C_5 resonance. Ribosylation of compound **7** therefore results in an upfield shift of 3.8 ppm for the C_5 resonance while the chemical shifts of the C_6 resonance both before and after ribosylation are identical. The glycosylation site in compound **8** must be the N-4 position and not N-2 because of this large effect at C_5.

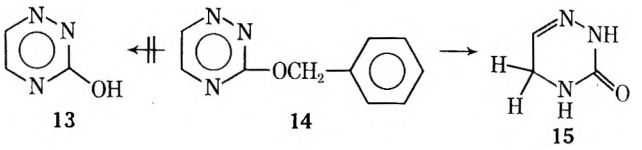
The assignment of this structure for compound **8** is confirmed by examining the α and β substitution shifts when compared with the *as*-triazin-3-one 1-oxide anion. This anion was formed by neutralization of compound **7** by LiOH in Me_2SO. Large upfield shifts of 13.6 and 11.5 ppm were observed for the adjacent C_5 resonance and the carbonyl resonance of the nucleoside **8** as compared to the triazine anion, while the C_6 resonance exhibited a downfield shift of 2.0 ppm. These shift changes are of the same order of magnitude and direction as α and β substitution shifts reported for other heteroaromatic systems,[13,14] that is, large upfield α values and small negative β shifts.

The ease of reduction of the triazine ring of the nucleosides **6** and **8** to yield 2,5-dihydro-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*as*-triazin-3(4*H*)-one (**11**) and the analogous deblocked nucleoside **12** is of interest, since the reduction of the structurally related 6-azauridine is much more difficult.[17,18] Attempts to prepare 3-hydroxy-*as*-triazine (**13**)[10] by hydrogenation of 3-benzyloxy-*as*-triazine (**14**) furnished only the reduced product 2,5-dihydro-*as*-triazin-3(4*H*)-one (**15**), the parent heterocycle of nucleosides **11** and **12** (Scheme II).

As noted previously, the anomeric proton in 4-β-D-ribofuranosyl-*as*-triazin-3(4*H*)-one 1-oxide (**8**) displayed an unusually small coupling constant in the pmr spectrum (broad singlet in DMSO, J = 2 Hz in D_2O). Reduction of the aglycon, however, produced a nucleoside **12** which displayed a more "normal" coupling constant ($J_{1',2'}$ = 5.5 Hz in D_2O) for the anomeric proton. It was thus apparent that the *as*-triazin-3-one 1-oxide ring was strongly affecting the anomeric proton. Such an effect on the $H_{1',2'}$ coupling constant could be due to an altered conformation of the pentofuranose ring and thus to an altered $H_{1',2'}$ dihedral angle, a phenomenon described as a "steric effect." Alternatively, the aglycon could influence the $H_{1',2'}$ coupling constant *via* an electronic effect without significantly changing the conformation of the pentofuranose ring of **8** as compared to **12**, or a combination of both effects could be operative. That the vicinal coupling constant on saturated carbons is dependent on the electronegativity of the substituents on those carbons, in addition to the dependency on the dihedral angle as described by the familiar Karplus relationship,[19] has been well documented.[20-22] While an unusual steric effect of the aglycon on the pentofuranose ring in compound **8** cannot be ruled out, it is certainly not indicated by inspection of molecular models. Furthermore, such a steric effect would be unlikely to operate in **8** but not in the reduced nucleoside **12**. On the other hand, pK_a measurements of the corresponding aglycons **7** and **15** clearly show the very large difference in the electronic character of the two ring systems. The acidic pK_a of **7** was found to be 4.60, an extremely low pK_a value in comparison with the pK_a values of most purine and pyrimidine bases, while the pK_a of the reduced ring, 2,5-dihydro-*as*-triazin-3(4*H*)-one (**15**), was found to be greater than 11. The possibility of a correlation between the acidity of the aglycon and the $H_{1',2'}$ coupling constant is supported by the recently published data of Nesnow, *et al.*[23] These authors reported a broadened singlet for the anomeric proton of 4-hydroxy-5-fluoro-1-β-D-ribofuranosyl-2-pyridone (5-fluoro-3-deazauridine) while the anomeric proton of 3-deazauridine[24] appears as a doublet, J = 2.5 Hz. In this example too, it is hard to envision a steric effect between the aglycon and the sugar, while the electronic character of the aglycons is quite different as reflected by the difference in the acidic pK_a of these two nucleosides. pK_a values of 6.5 and 4.5 are reported for 3-deazauridine[24] and 5-fluoro-3-deazauridine,[23] respectively.

The interesting antitumor properties of 4-β-D-ribofuranosyl-*as*-triazin-3(4*H*)-one 1-oxide (**8**) have been communicated separately elsewhere.[25]

SCHEME II



13 14 15

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Experimental Section

General.—Nmr spectra were recorded on a Hitachi Perkin-Elmer R-20A spectrometer in $CDCl_3$ (TMS), deuterated DMSO (DSS), or D_2O (DSS) with the appropriate internal standards. Uv spectra were determined on a Cary 15 ultraviolet spectrophotometer, and mass spectra were recorded on a Perkin-Elmer 270 mass spectrometer. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus, and are uncorrected. Evaporations were performed under reduced pressure on a rotary evaporator. Thin layer chromatography was performed on Analtech precoated (250 μ) silica gel GF plates, and the spots were visualized by irradiation with a Mineralight uv lamp. Column chromatography was carried out utilizing the method of Loev and Goodman[26] in plastic tubes (purchased from J. T. Baker) transparent to uv light. The tubes were packed with silica gel powder (Baker catalog #3405) containing 1% zinc silicate fluorescent indicator (Baker catalog #2101). The compounds were applied to the column preabsorbed on silica gel. This was accomplished by adding silica gel to a solution of the compounds followed by evaporation to dryness. The columns were then eluted with the appropriate solvent. The position of the bands on the column was visualized by irradiation with Mineralight uv lamp. These columns are referred to in the text as "dry columns." pK_a values were measured by alkalometric titration with 0.005 N NaOH performed on a Radiometer Autoburette ABU 12 coupled to Radiometer Titrator 11 and Radiometer Titrigraph. Elemental analyses were performed by Heterocyclic Chemical Corp., Harrisonville, Mo. 64701.

3-Methoxy-*as*-triazine 1-Oxide (3).—To a solution of 4 (7.5 g, 0.0675 mol) in C_6H_6 (520 ml) was added *m*-chloroperbenzoic acid (purchased from K & K Laboratories Inc., 37.0 g, 0.182 mol active ingredient) and the resulting mixture was refluxed for 24 hr. C_6H_6 was then evaporated, the residue was dissolved in $CHCl_3$, and the $CHCl_3$ solution was extracted three times with saturated Na_2CO_3 solution. After drying (Na_2SO_4) the mixture was applied to a dry column of silica gel and eluted with $CHCl_3$–EtOAc (9:1). The main uv-absorbing component was vacuum sublimed (65°, 0.2 mm) to give **3** (2.576 g, 30.0%). Resublimation raised the melting point to 70–72°, identical with that reported by Paudler and Chen.[7]

4-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-*as*-triazin-3(4*H*)-one 1-Oxide (6) and *as*-Triazin-3(4*H*)-one 1-Oxide (7).—To a solution of halogenose 5 [freshly prepared from 10.08 g (20 mmol) of 2,3,5-tri-*O*-benzoyl-1-*O*-acetyl-D-ribofuranose][27] in CH_3CN (100 ml) was added **3** (2.04 g, 16 mmol). The resulting clear solution was allowed to stand without stirring. After 1 week the mixture of crystals deposited from this solution was filtered off and the filter cake was treated with hot $CHCl_3$ (1 l.). The $CHCl_3$-insoluble crystals of **7** were removed by filtration and recrystallized from H_2O to give 0.195 g (10.8%), mp 228–230° dec. Recrystallization from H_2O furnished a sample for analysis: mp 234° dec; uv $\lambda_{max}^{H_2O}$ 256, 337 nm (ε 6780, 5880); $\lambda_{max}^{pH\ 1}$ 264, 337 nm (ε 7000, 5320), $\lambda_{max}^{pH\ 11}$ 252, 335 nm (ε 7240, 6350); nmr (deuterated DMSO) 8.22 (d, J = 5 Hz), 7.70 ppm (d, J = 5 Hz); mass spectrum molecular ion at m/e 113 and characteristic peak at m/e 97 owing to loss of oxygen from the NO function.

Anal. Calcd. for $C_3H_3N_3O_2$: C, 31.87; H, 2.67; N, 37.16. Found: C, 31.75; H, 2.67; N, 36.92.

The hot $CHCl_3$ solution obtained above was concentrated, EtOH was added, and after standing at 25° for 12 hr white fluffy crystals of **6** were collected and recrystallized from $CHCl_3$–EtOH to give pure **6** (3.40 g, 42.5%), mp 236–238°, $[\alpha]^{22}D$ +31° (c 1.0, $CHCl_3$). The yield of **7** varied in different batches between 0 and 30%, but the yield of **6** based on **3** not converted to **7** was consistently 40–45%.

Anal. Calcd for $C_{29}H_{23}N_3O_9$: C, 62.47; H, 4.15; N, 7.53. Found: C, 62.49; H, 4.25; N, 7.34.

4-β-D-Ribofuranosyl-*as*-triazin-3(4*H*)-one 1-Oxide (8).—To a suspension of **6** (1.70 g, 3.05 mmol) in anhydrous MeOH (60 ml) was added a solution of $NaOCH_3$ (0.486 g, 9.0 mmol) in anhydrous MeOH (50 ml) and the mixture was stirred for 5 hr. Dowex 50 WX8 ion exchange resin (H^+ form, 18 ml wet volume in MeOH) was added to the clear solution and stirring was continued for 10 min. The ion exchange resin was removed by filtration, the MeOH solution was concentrated to a few milliliters, and Et_2O (150 ml) was added. After standing overnight, crystalline **8** (0.576 g, 77%) was collected by filtration and washed with large amounts of Et_2O, mp 172–173° dec. Two recrystallizations from MeOH furnished a sample for analysis: mp 174–176° dec; uv $\lambda_{max}^{H_2O\ and\ pH\ 1}$ 207, 267, 343 nm (ε 16,750, 8510, 7640); $\lambda_{max}^{pH\ 11}$ 232, 273, 340 nm (ε 9380, 6640, 740); nmr (deuterated DMSO) 8.78 (d, J = 5.5 Hz), 7.80 (d, J = 5.5 Hz), 5.78 (broad singlet), 4.10 ppm (multiplet); $[\alpha]^{22}D$ +229° (c 1.0, H_2O). Characteristic peaks in the mass spectrum were those at m/e 133 and 113 (cleavage of the glycosidic bond) and at m/e 97 (loss of oxygen from the NO function).

Anal. Calcd for $C_8H_{11}N_3O_5$: C, 39.18; H, 4.52; N, 17.13. Found: C, 39.33; H, 4.50; N, 17.20.

2,5-Dihydro-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*as*-triazin-3(4*H*)-one (11).—Into a suspension of **6** (0.800 g, 1.435 mmol) and 5% Pd-on-charcoal catalyst (0.080 g) in $CHCl_3$ (200 ml) was bubbled H_2 for 90 min. The catalyst was then removed by filtration, and the clear solution was concentrated to dryness. The residual oil was applied to a dry column of silica gel and eluted with $CHCl_3$–EtOAc (9:1) to give **11** (0.684 g, 87.5%). Rechromatography furnished a sample for analysis, mass spectrum molecular ion at m/e 543.

Anal. Calcd for $C_{29}H_{25}N_3O_8$: C, 64.08; H, 4.63; N, 7.73. Found: C, 64.05; H, 5.14; N, 7.46.

2,5-Dihydro-4-β-D-ribofuranosyl-*as*-triazin-3(4*H*)-one (12). Method A.—Syrupy **11** (0.360 g, 0.663 mmol) was dissolved in 25 ml of ethanolic NH_3 (saturated at 0°). After standing in a pressure bottle at 25° for 3 days the solvent was evaporated and the residue was dissolved in H_2O and $CHCl_3$. The aqueous layer was extracted with $CHCl_3$ and concentrated to dryness and the residue was dried by coevaporation with EtOH *in vacuo*. The residual oil was applied to a dry column of silica gel and eluted with the upper phase of EtOAc–*n*-PrOH–H_2O (4:1:2) to give **12** as an oil (0.115 g, 75%), one spot on silica plates with the above mentioned solvent system (R_f 0.27): λ_{max}^{MeOH} 215 and 245 nm; nmr olefinic proton at 7.10 (pseudotriplet), anomeric at 5.85 (d, J = 5.5 Hz), CH_2 protons of the heterocycle at 3.74 ppm (pseudodoublet). On irradiation of the latter, the signal at 7.10 ppm collapsed to a sharp singlet. The mass spectrum showed a molecular ion at m/e 231.

Anal. Calcd for $C_8H_{13}N_3O_5$: C, 41.55; H, 5.66; N, 18.17. Found: C, 41.51; H, 5.87; N, 17.89.

Method B.—To a solution of **8** (0.245 g, 1 mmol) in 50 ml of EtOH was added 5% Pd on charcoal (0.025 g) and H_2 gas was bubbled into the rapidly stirred mixture. After 1 hr the catalyst was removed by filtration, and the EtOH was evaporated to give a syrup which was chromatographed on a dry column of silica gel as described for the preparation of **12** from **11**. The product (0.195 g, 84.5%) was identical in every respect with that of method A.

4-β-D-Ribofuranosyl-*as*-triazin-3(4*H*)-one (10).—Blocked nucleoside **6** (0.900 g, 1.62 mmol) was treated with 120 ml of ethanolic ammonia (saturated at 0°) in a pressure bottle at 25° for 5 days. After evaporation of the solvent the brown residue was dissolved in H_2O (100 ml) and was extracted three times with $CHCl_3$ (80 ml each). The aqueous phase was evaporated to dryness, and the residue was dissolved in H_2O (25 ml) and filtered from insoluble material. The solution was evaporated to dryness again and the brown residue was crystallized from EtOH to give **10** (0.160 g, 43.2%). Two recrystallizations furnished a sample (yellow powder) for analysis, for uv see Table I. This compound appeared to be unstable on prolonged standing, and the signals in the nmr spectrum were unusually broadened, indicating possible decomposition in the solvent, deuterated DMSO.

Anal. Calcd for $C_8H_{11}N_3O_5$: C, 41.92; H, 4.83; N, 18.33. Found: C, 41.97; H, 4.86; N, 18.41.

***as*-Triazin-3(4*H*)-one 1-Oxide (7) by Acid Hydrolysis of 3.**—To a solution of **3** (0.100 g, 0.788 mmol) in CH_3CN (5 ml) was added dilute methanolic HCl (0.5 N, 0.125 ml) and the solution was allowed to stand for several days. The crystalline material deposited from this solution was recrystallized from H_2O to give **7** (0.004 g, 4.5%); melting point and uv were identical with those of the analytically pure sample of **7** described above.

3-Benzyloxy-*as*-triazine (14).—Sodium metal (1.1 g, 48 mmol) was dissolved in benzyl alcohol (100 ml), and 3-methylthio-

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as-triazine[28] (5.08 g, 40 mmol) was added. After 24 hr stirring at 25° Dry Ice was added, and the solution containing some precipitate was concentrated *in vacuo* to 40 ml. After dilution with C_6H_6 the precipitate was removed by filtration and the solution was concentrated to dryness. The residue was vacuum distilled [bp 120° (0.3 mm)] to give pure **14** as crystals (1.58 g, 21%), mp 69–70°.

Anal. Calcd for $C_{10}H_9N_3O$: C, 64.15; H, 4.84; N, 22.44. Found: C, 64.13; H, 4.82; N, 22.31.

2,5-Dihydro-*as*-triazin-3(4*H*)-one (15).—To a solution of **14** (0.561 g, 3 mmol) in DMF (40 ml) was added 5% Pd on charcoal (50 mg), and H_2 was bubbled into the solution for 90 min. The catalyst was then removed by filtration and the solvent was evaporated. The residual white powder was crystallized from EtOH to give **15** (0.18 g, 60.5%), mp 135–136°. Concentration of the EtOH mother liquor yielded an additional 0.065 g (combined yield 82%). An analytically pure sample was obtained by recrystallization from EtOH: mp 136–137°; λ_{max}^{MeOH} 243 nm (ϵ 2440); nmr (D_2O) 7.01 (t, J = 3 Hz), 4.02 (d, J = 3 Hz); mass spectrum molecular ion at m/e 99.

Anal. Calcd for $C_3H_5N_3O$: C, 36.36; H, 5.08; N, 42.40. Found: C, 36.39; H, 5.04; N, 42.30.

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Acknowledgment.—The authors wish to thank Mr. E. Banta, Mr. L. T. Larek, and Mr. D. M. Capampangan for the instrumental data.

Registry No.—**3**, 27531-67-5; **4**, 28735-22-0; **5**, 22860-91-9; **6**, 40919-31-1; **7**, 40919-32-2; **8**, 40919-33-3; **10**, 40919-34-4; **11**, 40919-35-5; **12**, 40919-36-6; **14**, 40919-37-7; **15**, 40919-38-8.

Peripheral Synthesis of Secondary Medium-Ring Nitrogen Heterocycles[1]

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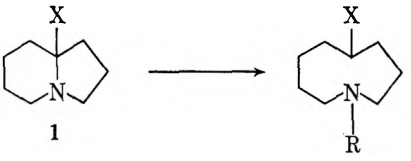
Received January 11, 1973

Three methods for preparing secondary azacyclononanes from 9-substituted indolizidines were investigated. The first method utilized previously developed ring-opening reactions to give *N*-benzylazacyclononanes, which were debenzylated by cleavage with alkyl chloroformates. *N*-Benzyl-5-ethylideneazacyclononane (**8**) was converted to **11** in this way *via* either the ethyl or the 2,2,2-trichloroethyl carbamate. The former group was removed with methyllithium and the latter with zinc dust. Only this latter sequence was successful for debenzylating *N*-benzyl-5-(2′-phenylethylidene)azacyclononane (**12**) to **17**. The second method involved direct cleavage of 9-vinylindolizidine (**3**) and 9-benzylindolizidine (**22**) with ethyl or phenyl chloroformate. Catalytic reduction and hydrolysis of the carbamate from **3** gave **19**. Hydrolysis of the carbamate from **22** caused transannular cyclization back to the starting material. In the final method, **3** was treated with $LiAlH_4$ and $NiCl_2$ to give 9-ethylindolizidine (**20**) and 5-ethyl- (**19**), 5-vinyl- (**10**), and 5-ethylideneazacyclononane (**11**) in varying proportions depending on the reaction conditions. All the secondary amines prepared in this study were converted to the known *N*-methyl homologs.

The peripheral synthesis of medium-ring azacycles as developed in our laboratory[3–5] leads exclusively to compounds in which the ring nitrogen is tertiary (eq 1, R = CH_3). While such compounds are of interest because of their relation to certain alkaloids[6,7] as well as their ability to undergo transannular reactions,[8,9] the availability of the corresponding secondary amines would provide additional possibilities for studies in these areas. At the time this project was initiated the preparation of secondary medium-ring azacycles was limited to two general methods: the ring expansion of cycloalkanones,[10] and the electrolysis of β-keto-1-azabicycloalkanes.[11] Although both of these syntheses are somewhat limited in scope by the availability of starting materials or the reaction conditions, a potentially general route has been described[12] more recently which nicely complements those to be discussed in this paper.

As before[3–5] our method involves the selective cleavage of the central carbon–nitrogen bond of bridgehead-substituted 1-azabicycloalkanes (eq 1), which in the



(1)

present study were restricted to the readily available[4,5,13] 9-substituted indolizidines (**1**). Selectivity was assured by the nature of the 9 substituent and the cleavage was facilitated by quaternization of the nitrogen atom. The three methods to be described can be classified according to the character and fate of this quaternary stage: (1) the quaternary compound gives a tertiary amine which is subsequently dealkylated; (2) the quaternary intermediate yields a derivative which can be converted to the secondary amine; or (3) the quaternary intermediate decomposes directly to the secondary amine.

The first method is based on the previously described[3–5] successful synthesis of *tertiary* medium-ring azacycles and requires the selective dealkylation of these compounds to the desired secondary amine. The reaction chosen for this purpose, the chloroformate ester cleav-

(1) Taken in part from the Ph.D. Dissertation of R. G. Daubert, Texas Christian University, 1971.

(2) National Science Foundation Trainee, 1966–1970.

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(13) An improved preparation of one of the precursors of these starting materials, 9-cyanoindolizidine (**2**), is described in the Experimental Section.

age of tertiary amines to a carbamate and an alkyl chloride (eq 2), is very similar in mechanism and scope

$$R_3N + ClCOOR' \longrightarrow [R_3NCOOR']^+ Cl^- \longrightarrow R_2NCOOR' + RCl \quad (2)$$

to the well-known von Braun cyanogen bromide reaction (eq 3)[14] but has the advantage of permitting

$$R_3N + BrCN \longrightarrow [R_3NCN]^+ Br^- \longrightarrow R_2NCN + RBr \quad (3)$$

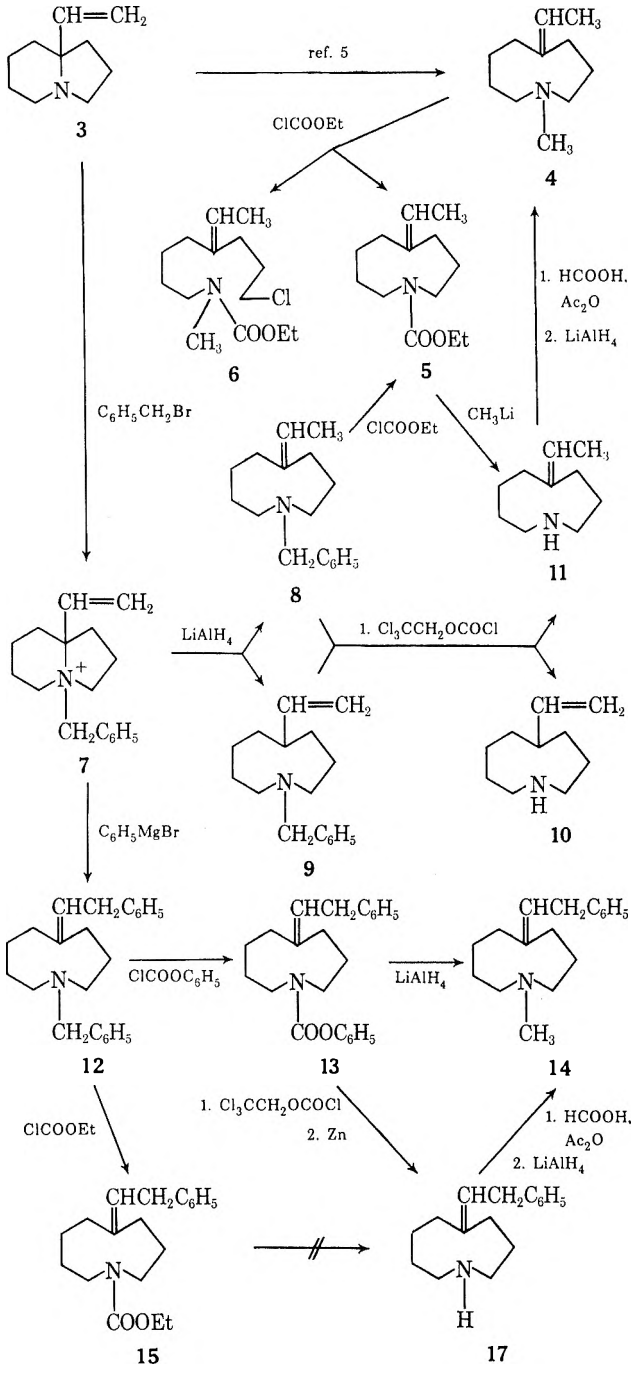
variations in the alcohol moiety (R′) and thus in the method of ultimately converting the carbamate to the secondary amine. Although this chloroformate cleavage has been known for some time in the alkaloid field,[15,16] other applications and studies[17-21] are limited, and therefore the more thoroughly investigated von Braun reaction[14] was used as a model.

The first compound investigated was *N*-methyl-5-ethylideneazacyclononane (**4**), prepared[13] from 9-vinylindolizidine (**3**) by our previously reported[5] methods. Since the von Braun reaction is known to be nonselective for N-demethylation of related compounds,[12] it was not unexpected that the ethyl chloroformate cleavage of **4** gave almost equal amounts of the demethylated product **5** and a ring-opened product (**6** or the other possible isomer).

What is obviously necessary to increase the selectivity of the N-dealkylation is a more labile group on nitrogen. Both the 3,3-ethylenedioxybutyl[12] and the benzyl group[22,23] have been used for this purpose. The former group[12] is cleaved by acid hydrolysis and hydrazinolysis while the latter is removed by hydrogenolysis.[22,23] Although the latter reaction would interfere with the retention of unsaturation in the product, the benzyl group was nevertheless chosen, because it can be introduced more efficiently[12] and because it was anticipated[24] that it could be removed easily by the chloroformate cleavage.

An expected limitation of the *N*-benzyl group was that N-debenzylation would compete with the ring opening of the bicyclic quaternary ammonium salt precursors.[3-5] However, treatment of the *N*-benzyl quaternary salt of 9-vinylindolizidine (**7**) with $LiAlH_4$ gave only a trace of the N-debenzylation product **3**. The major product, 5-ethylidene-*N*-benzylazacyclononane (**8**), was identified from its spectral characteristics, analysis of its benzyl bromide salt, and its ultimate conversion (*vide infra*) to the known[5] *N*-methyl compound **4**. This occurrence of allylic rearrangement during ring opening parallels the behavior of the *N*-methyl analog.[5] A minor product was probably[5] the vinyl isomer **9**, as shown by debenzylation (*vide infra*) of the mixture to a mixture of the 5-vinyl and 5-ethylidene secondary amines **10** and **11**, respectively.

Reaction of **8** with ethyl chloroformate gave the same carbamate, **5**, obtained from cleavage of the *N*-methyl compound **4** but none of the ring-opened isomer **6**. Because of difficulties with transannular ring-closure during the hydrolytic removal of the carbamate group from an unsaturated medium-ring compound (*vide infra*), a method based on the known[25] reaction of amides with lithium reagents was utilized. The desired 5-ethylideneazacyclononane (**11**) was by far the major portion (93%) of the product of **5** and methyllithium, presumably[25] because the secondary amine was tied up as a lithium salt of the carbinolamine intermediate until work-up and hence resistant to cyclization. The structure of **11** was proven by its spectral properties, the analysis of its styphnate, and its conversion to the known[5] *N*-methyl derivative **4** by formylation and reduction. The overall yield of **3** → **11** approaches



(14) H. A. Hageman, *Org. React.*, **7**, 198 (1965).
(15) J. Gadamer and F. Knoch, *Arch. Pharm. (Weinheim)*, **259**, 135 (1921).
(16) J. Knabe, *Arch. Pharm. (Weinheim)*, **289**, 479 (1956).
(17) J. Knabe and H. Gohmert, *Arch. Pharm. (Weinheim)*, **303**, 525 (1970) and previous papers in this series.
(18) J. A. Campbell, *J. Org. Chem.*, **22**, 1259 (1957).
(19) W. B. Wright, Jr., and H. J. Brabander, *J. Org. Chem.*, **26**, 4057 (1961).
(20) J. D. Hobson and J. G. McCluskey, *J. Chem. Soc. C*, 2015 (1967).
(21) M. M. Abdel-Monem and P. S. Portoghese, *J. Med. Chem.*, **15**, 208 (1972).
(22) R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken, *J. Org. Chem.*, **33**, 3187 (1968).
(23) N. J. Leonard and T. Sato, *J. Org. Chem.*, **34**, 1066 (1969).
(24) R. Ruggli and G. Geiger, *Helv. Chim. Acta*, **30**, 2035 (1947).
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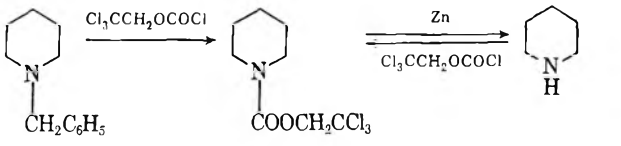
50%, which is highly competitive with methods[12] leading to secondary medium-ring azacycles without the potentially useful transannular unsaturation.

As a further example of the utility of this route, the quaternary salt **7** was treated with phenyl Grignard reagent in an abnormal displacement reaction[5] to give the phenylethylidene derivative **12** in good yield. The structure of **12** follows from its spectral properties, the analysis of its methiodide, and its conversion, by the $LiAlH_4$ reduction of the phenyl carbamate **13**, to the known[5] *N*-methyl compound **14**. The debenzylation of **12** to either the phenyl (**13**) or the ethyl (**15**) carbamate proceeded without any evidence for ring opening. A preliminary experiment indicated, as expected, that acid hydrolysis of **13** gave considerable (*ca.* 70%) cyclization products. Consequently, the methyllithium procedure was applied to the ethyl carbamate **15**. Unfortunately, in this instance considerable polymer and a complex mixture of conjugated and unconjugated olefins were obtained. Presumably the lithium reagent causes isomerization of the double bond of **15** and subsequent polymerization of the resultant styrene derivative.

In order to debenzylate such apparently sensitive olefins as **12** another, more labile, carbamate would be desirable. A recently reported possibility, the β,β,β-trichloroethyl carbamate, can be removed with zinc dust in methanol,[26] conditions which should not affect double bonds. The question of whether the corresponding chloroformate has the same ability to debenzylate tertiary amines as the ethyl and phenyl chloroformates was answered by cleaving *N*-benzylpiperidine to the β,β,β-trichloroethyl carbamate **16** in



16

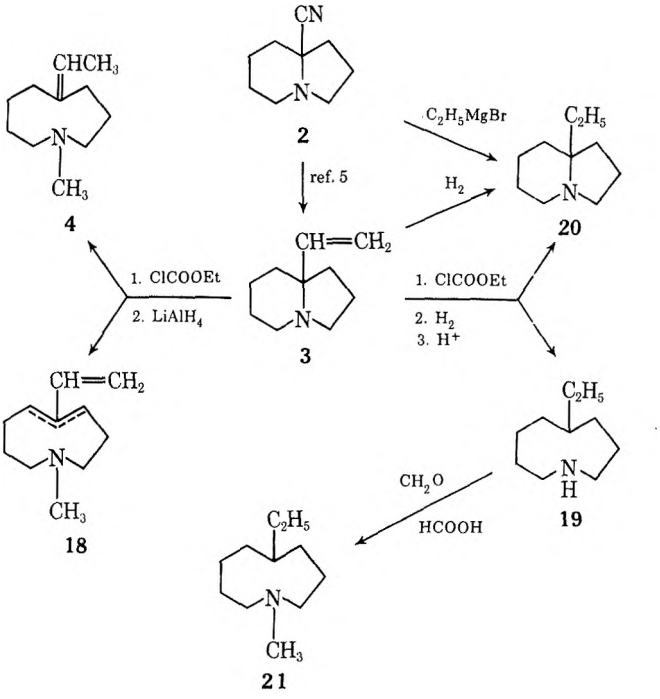
excellent yield. This carbamate, also available from piperidine and the chloroformate, could be cleaved to piperidine by the reported[26] method.

Application of this sequence to the phenylethylidene compound **12** leads to the desired secondary amine **17** in 76% crude yield (71% overall from **3**) as an approximately equal mixture of geometrical isomers. The structure of **17** (mixture) follows from its vpc and spectral data, its analysis, and its conversion in 76% yield to the known[5] *N*-methyl compound **14**, which does not show any evidence of geometrical isomers.

As a final test of this last debenzylation method a mixture of **8** and **9** (86:14) was converted to an 87:13 mixture of the previously prepared secondary amines **11** and **10** in 77% yield. This constitutes an overall yield of *ca.* 63% from the bicyclic precursor **3** and testifies as to the efficiency of this method for the synthesis of unsaturated secondary medium-ring azacycles.

Ring-opening method 2 can be considered a simplified variation of method 1 just described in which the chloroformate cleavage is carried out directly on the indolizidine **1** to give the medium-ring carbamate (eq 1, R = COOR). Based on the von Braun reaction[14] as a model it was anticipated that simple indolizidines would react with chloroformates to open the pyrrolidine ring,[27] but that *N*-allyl groups generally[14] would be cleaved more readily than saturated alkyl groups. Therefore 9-vinylindolizidine (**3**) once again was chosen as a substrate to test the feasibility of this method.

Reaction of **3** with ethyl chloroformate gave a mixture of carbamates which was directly reduced[20] with lithium aluminum hydride to give a 60:40 mixture of N-methylated amines in about 50% overall yield. The minor component was identified as the known[5] ethylidine amine **4** and the spectral characteristics of the major product suggested that it was the conjugated diene **18** presumably formed by elimination of HCl from an intermediate carbamate or quaternary salt. Catalytic reduction of the above carbamate mixture followed by acid hydrolysis gave 5-ethylazacyclononane (**14**) in 47% yield along with a small amount of 9-ethylindolizidine (**20**). The structure of the former compound follows from its analysis, spectral properties, and its conversion to the known[5] *N*-methylamine **21**.



The latter compound was identified as 9-ethylindolizidine (**20**) by comparison of its infrared spectrum with those of samples synthesized by catalytic reduction of the 9-vinyl compound **3** or by the reaction of the ethyl Grignard reagent with the cyano derivative **2**. 9-Ethylindolizidine (**20**) probably arises from the acid-catalyzed cyclization of residual unsaturated secondary amines analogous to the process observed for closely related tertiary amines.[28,29] Substitution of phenyl chloroformate for ethyl chloroformate in the reaction with **3** gave essentially identical results.

In an attempt to direct the apparent tendency toward diene formation noted above in such a way that only a single cleavage product would be produced, the reaction of 9-benzylindolizidine (**22**) with phenyl chloro-

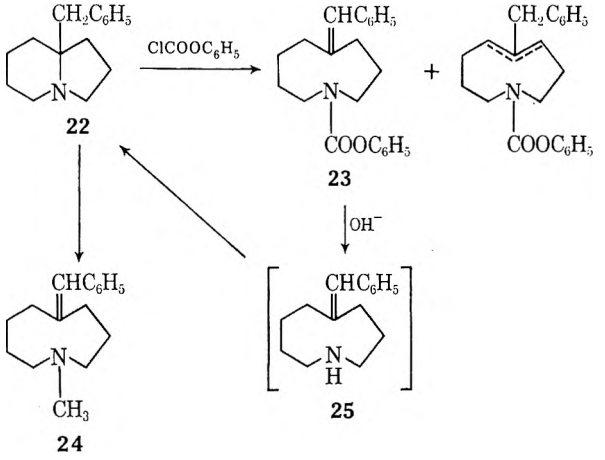
(26) T. B. Windholz and D. B. R. Johnston, *Tetrahedron Lett.*, 2555 (1967).

(27) E. Ochiai and K. Tsuda, *Chem. Ber.*, **67**, 1011 (1934).

(28) K. Schofield and R. J. Wells, *Chem. Ind. (London)*, 572 (1963).

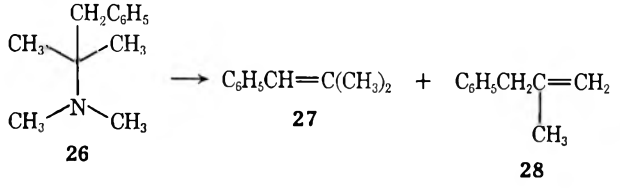
(29) A. J. Sisti and D. L. Lohner, *J. Org. Chem.*, **32**, 2026 (1967).

formate was examined. Once again by analogy to the von Braun reaction[14,30] the tertiary alkyl group should be cleaved preferentially with formation of an olefinic product. This product should consist of the single conjugated olefin **23** as suggested by the exclusive formation of the benzylidene isomer **24** from the β-elimination of **22** MeI.[3,4] Unfortunately, the nmr spectrum of the crude phenylcarbamate from **22** clearly showed the presence of two olefins, a result which was substantiated by the vpc detection of two $LiAlH_4$ reduction products in 70:30 ratio. The phenyl carbamate mixture was treated with strong base on the presumption that isomerization to a single olefin might occur. The only product found, however, was the original starting material **22**, apparently formed by transannular cyclization of an intermediate secondary amine such as **25**.



Analogous anionic additions of amines to phenyl conjugated hydrocarbons are known.[31]

In order to determine if the nonselectivity of the above chloroformate cleavage is inherent in the reaction or peculiar to the ring system, a simple acyclic model, *N*,*N*-dimethyl-α,α-dimethyl-β-phenethylamine (**26**), was treated with phenyl chloroformate. The olefinic product consisted of almost equal amounts of the conjugated and the nonconjugated alkenes, **27** and **28**, thereby establishing that the lack of selectivity of this reaction limits the utility of this second method to the preparation of saturated medium-ring compounds.



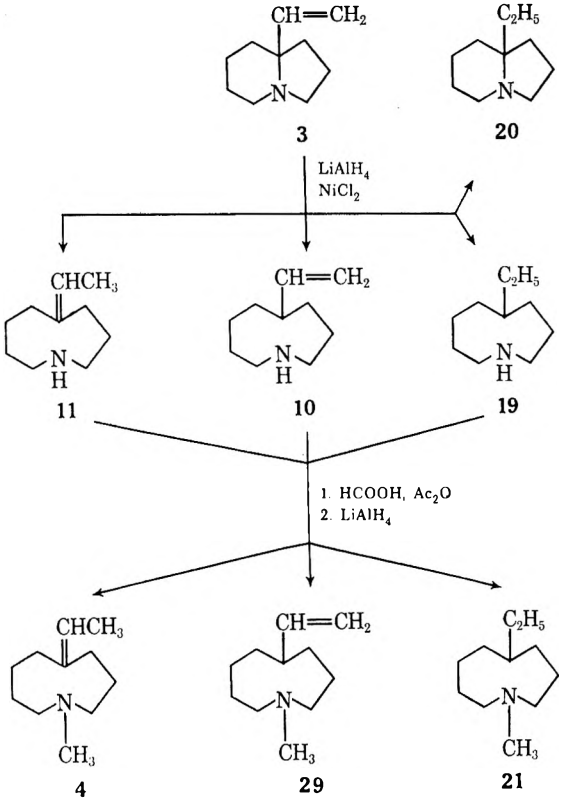
The third and final method investigated for preparing secondary medium-ring amines is based on the reductive cleavage of allyl groups from *N*-allyl-*N*-alkylanilines with lithium aluminum hydride and nickel chloride.[32] Under the reported conditions 9-vinylindolizidine (**3**) failed to react (Table I, no. 1), presumably[32] because of its high basicity compared to anilines. With an increased ratio of nickel chloride to amine, however, reaction did occur to give a mixture of bicyclic (**20**) and medium-ring amines (**10**, **11**, **19**) some of which contained rearranged (**11**) or reduced (**19**) double bonds. The products were identified by comparison with previously prepared samples and by formylation and reduction of the reaction mixture to give a mixture of the known *N*-methyl amines, **4**, **21** and **29**.

TABLE I

REACTIONS OF 9-VINYLINDOLIZIDINE (**3**) WITH $LiAlH_4$ AND $NiCl_2$

No.	Equiv of $LiAlH_4$	Equiv of $NiCl_2$	Time, hr	Rel % of **3**	**20**	**19**	**10**	**11**	Wt % yield
1[a]	4.8	0.3	138	100					
2[a]	3.0	0.8	91	55	15		12[b]	18	60
3[a]	7.6	1.2	22		86		10[b]	4	60
4[a]	7.6	1.2	110	15	21		3[b]	61	85
5[a]	10.0	1.2	103		7		88	5	42
6	7.7	2.3	12	37	34	15	4	10	50
7	7.7	2.3	16	30	45	11	3	11	75
8	7.7	2.4	24		74		20[b]	6	80
9	7.6	2.3	113	Trace	41	7	12	40	70
10[c]	7.6	2.4	16			35	8	51	77
11[a,d]	7.7	1.2	112		100				81

[a] Procedure differs in that $LiAlH_4$ was added to refluxing mixture of $NiCl_2$ and THF. [b] Vpc analyses performed with column A which does not separate **10** and **19**. [c] Reactant was 87:13 mixture of **11**:**10**; two unidentified peaks also present in product. [d] Reactant was **20**.



The product distribution from the Tweedie reaction of **3** was very sensitive to the experimental conditions (Table I) and not always reproducible in our hands, probably owing to variations in the nickel catalyst. The unsaturated medium-ring compounds **10** and **11** were never obtained in good yield free of other products, although the saturated amine **19** could be by using a large excess of $LiAlH_4$ (Table I, no. 5). It therefore appears that the utility of this method for preparing

(30) R. C. Elderfield and H. A. Hageman, *J. Org. Chem.*, **14**, 605 (1949).
(31) R. C. Bansal, E. J. Eisenbraun, and P. W. Flanagan, *J. Amer. Chem. Soc.*, **88**, 1837 (1966).
(32) V. L. Tweedie and J. C. Allabashi, *J. Org. Chem.*, **26**, 3676 (1961)

secondary medium-ring amines will also be restricted to saturated examples.

Experimental Section

Melting points and boiling points are uncorrected. Analyses were performed by M-H-W Laboratories, Garden City, Mich. Nmr spectra were determined on a Varian A-60A instrument in CCl_4 or C_2Cl_4 with TMS as an internal standard. Ir spectra were recorded on a Perkin-Elmer 237 infrared spectrophotometer as thin films for liquids or KBr disks for solids. Vpc analyses were performed on a Beckman GC-2A gas chromatograph utilizing column A (4 ft × 0.25 in., 20% SE-30 on Chromosorb W) or column B (15 ft × 0.25 in., 5% KOH and 15% polyphenylether-6-ring on Chromosorb W) unless otherwise noted.

9-Cyanoindolizidine (2).—To a stirred solution of 100 g of mercuric acetate in 400 ml of 5% HOAc at 90° was added 9.0 g of freshly distilled indolizidine.[4,33] After 1 hr the reaction mixture was cooled to 0°, the mercurous acetate was removed by filtration, and a solution of 22.4 g of KCl in 100 ml of H_2O was added to the filtrate. The resulting mercuric chloride complex of the enamine was mixed with 100 ml of H_2O, and 10 ml of concentrated HCl was added followed by a solution of 39.2 g of NaCN in 100 ml of H_2O (*HOOD!*). The resulting solution was extracted with three 50-ml portions of ether which were combined, dried ($CaSO_4$), and concentrated to give 6.6 g (65%) of **2** whose ir spectrum is identical with that of a sample prepared by the lengthier and less efficient method[34] *via* the isolated iminium perchlorate.

Reaction of *N*-Methyl-5-ethylideneazacyclononane (4) with Ethyl Chloroformate.—After a mixture of 1.0 g of **4**[5] and 5.7 g of ethyl chloroformate in 25 ml of benzene had been heated under reflux for 16 hr, it was washed with two 30-ml portions of 4 *N* HCl, dried (K_2CO_3), and concentrated to give 1.2 g of a liquid whose vpc on a 4.5 ft 15% SE-30, 5% Carbowax 20M on Chromosorb W column indicated two products (52:48) of vastly different retention time (5 and 13.5 min at 220°). The former had the same retention time and nmr spectrum as **5**, the product from the ethyl chloroformate cleavage of **8**. The second product (**6**) had the following nmr spectrum: δ 5.2 (m, 1, C=CH_2), 4.0 (q, J = 7 Hz, 2, OCH_2), 3.3 (two overlapping t's, 4, CH_2N and CH_2Cl), 2.8 (s, 3, NCH_3).

***N*-Benzyl-5-ethylideneazacyclononane (8).**—After a mixture of 6.0 g of **3**[5] and 9.5 g of $PhCH_2Br$ had been allowed to react at room temperature for 24 hr, 280 ml of glyme and 6.0 g of $LiAlH_4$ were added and the solution was heated to reflux for 5 days. Excess $LiAlH_4$ was destroyed with H_2O, and the mixture was heated to reflux for 30 min and filtered. The combined filtrate and ether washings of the precipitate were dried (K_2CO_3) and concentrated at reduced pressure to give a liquid which was dissolved in 40 ml of 6 *N* HCl. The acid solution was washed with 25 ml of ether, basified with concentrated NaOH, and extracted with three 20-ml portions of ether. The combined ether extracts were dried (K_2CO_3) and concentrated to give 7.6 g (79%) of a liquid, bp 112° (0.25 mm), which gave two peaks (86:14) on vpc analysis (column A). The major product had ir 3090, 3060, 3030, 1655, 1600, 730, 710, 690 cm^{-1}; nmr δ 7.2 (s, 5, PhH), 5.3 (q, J = 7 Hz, 1, C=CH), 3.5 (s, 2, NCH_2Ph). A benzyl bromide salt was prepared, mp 189.5–190.5° when heated at 2°/min.

Anal. Calcd for $C_{24}H_{32}NBr$ (**8**·$PhCH_2Br$): C, 69.55; H, 7.78; N, 3.38. Found: C, 69.76; H, 7.89; N, 3.41.

Reaction of *N*-Benzyl-5-ethylideneazacyclononane (8) with Ethyl Chloroformate. Preparation of 5-Ethylideneazacyclononane (11).—Using the procedure and work-up described above for **4**, 7.6 g of **8** and 16.8 g of ethyl chloroformate were allowed to react for 24 hr to give 8.3 g of **5**: ir 1700 cm^{-1}; nmr δ 5.3 (m, 1, C=CH), 4.1 (q, J = 7 Hz, 2, OCH_2), 3.25 (m, 4, CH_2N), 1.25 (t, J = 7 Hz, 3, CH_3). A solution of 4.1 g of **5** in 100 ml of benzene was added to 100 ml of 2.23 *M* CH_3Li in 100 ml of ether and the mixture was heated to reflux for 23 hr, at which time 70 ml of H_2O was added. The ether layer was extracted with two 25-ml portions of 6 *N* HCl which were basified with concentrated NaOH and extracted with two 50-ml portions of ether. Evaporation of the dried (K_2CO_3) ether extracts gave 1.9 g of a liquid whose major (93%) peak in the vpc had ir 3350 (NH), 1650 cm^{-1} (C=C); nmr δ 5.3 (m, 1, C=CH), 3.2 (m, 4, CH_2N). A styphnate was prepared, mp 151–152° (evacuated capillary).

Anal. Calcd for $C_{16}H_{22}N_4O_8$ (**11** styphnate): C, 48.24; H, 5.57; N, 14.06. Found: C, 48.10; H, 5.43; N, 14.10.

Methylation of 5-Ethylideneazacyclononane (11).—A 0.5-g sample of **11** (93%) was formylated with formic–acetic anhydride mixture and the resulting formamide was reduced with $LiAlH_4$ by the same procedures described (*vide infra*) for the product of the Tweedie reaction of **3**. A vpc of the 0.35 g of product on a 12 ft, 25% PPE on Chromosorb W column showed one major peak (90% of peak area) which was identified as **4** by comparison of its ir spectrum with that of an authentic sample.[5]

***N*-Benzyl-5-(2′-phenylethylidene)azacyclononane (12).**—A mixture of 5.0 g of **3**[5] and 7.4 g of $PhCH_2Br$ was allowed to react for 15 hr at room temperature and the resulting product was dissolved in 16 ml of CH_2Cl_2. This solution and 0.165 mol of PhMgBr in 155 ml of THF were mixed and heated under reflux for 3 days. Concentrated NH_4Cl solution was added until no precipitate remained, and the aqueous layer was extracted with two 50-ml portions of ether. The combined ether and THF solutions were extracted with 60 ml each of 3 *N* and 6 *N* HCl and the combined acid layers were saturated with KCl, basified with concentrated NaOH, and extracted with two 50-ml portions of benzene and 50 ml of ether. The combined organic extracts were dried (K_2CO_3) and concentrated to give 9.8 g (93%) of **12** as a viscous oil: ir 3075, 3050, 3020, 1600, 750, 695 cm^{-1}; nmr δ 7.2 (s, 5, PhH), 7.1 (s, 5, PhH), 5.4 (t, J = 6.5 Hz, 1, C=CH), 3.5 (s, 2, NCH_2Ph), 3.3 (d, J = 6.5 Hz, 2, C=CHCH_2Ph). A methiodide, mp 153–154° (evacuated capillary), was prepared.

Anal. Calcd for $C_{24}H_{32}NI$ (**12** MeI): C, 62.47; H, 6.99; N, 3.04. Found: C, 62.79; H, 7.21; N, 2.94.

Attempted N-Debenzylation of 12 with Ethyl Chloroformate and Methyllithium.—Application of the procedure used above for converting **8** to **11** to 9.6 g of **12** gave 5.3 g of a viscous red-brown oil which only partially distilled at 128° (0.25 mm). The distillate gave at least four peaks on vpc analyses and displayed two kinds of olefinic protons in the nmr (δ 6.5 and 5.5). The residue showed no olefinic protons in the nmr.

Reaction of 12 with Phenyl Chloroformate and $LiAlH_4$ to *N*-Methyl-5-(2′-phenylethylidene)azacyclononane (14).—Using the procedure described for **22** (*vide infra*) a 4.2-g sample of **12** and 10.3 g of PhOCOCl were allowed to react to give 6.0 g of crude **13** which was partially purified by passage through a short column of activity I Al_2O_3 with benzene–hexane. The resulting product had ir 3060, 3030, 1725, 1600, 750, and 685 cm^{-1}; nmr δ 7.12 (m, 10, PhH), 5.4 (m, 1, C=CH), 3.32 (m, 6, CH_2N, CH_2Ph).

A 1.5-g sample of **13** was reduced with $LiAlH_4$ as described for the ethyl carbamate of **3** to give 0.5 g of vpc-pure **14** whose ir spectrum was identical with that of an authentic sample.[5]

2,2,2-Trichloroethyl Piperidinecarbamate (16).—A mixture of 2.0 g of *N*-benzylpiperidine[35] and 7.3 g of 2,2,2-trichloroethyl chloroformate in 50 ml of benzene was heated under reflux for 2 days, 50 ml of ether was added, and the whole was washed with two 40-ml portions of 3 *N* HCl and 40 ml of H_2O. The organic layer was dried ($CaSO_4$) and concentrated to give 2.9 g (97%) of **16** as a liquid which crystallized upon standing. A vpc-collected sample (column A) had mp 35.5–37.5°; ir 1720, 850, 820, 775, 750, 715 cm^{-1}; nmr δ 4.8 (s, 2, Cl_3CCH_2[26]), 3.5 (m, 4, CH_2N). Identical spectra were obtained from a sample of **15** prepared from piperidine and the chloroformate.

Anal. Calcd for $C_8H_{12}NO_2Cl_3$ (**16**): C, 36.88; H, 4.64; N, 5.38. Found: C, 36.79; H, 4.45; N, 5.15.

Removal of Carbamate Group from 16.—A solution of 3.2 g of **16** in 50 ml of glacial HOAc and 3.3 g of zinc dust was stirred for 4 hr at room temperature. After removal of the zinc by filtration, the filtrate was basified with concentrated NaOH and extracted with three 50-ml portions of ether. The dried ether extracts were treated with picric acid in ether to give 1.7 g (44%) of piperidine picrate, mp 148.5–150.5°, identified by comparison of its ir spectrum with that of an authentic sample.

5-(2′-Phenylethylidene)azacyclononane (17).—After a solution of 6.0 g of **12** and 12.0 g of Cl_3CCH_2OCOCl in 50 ml of benzene had been heated to reflux for 17 hr, 50 ml of ether was added and the whole was washed with two 40-ml portions of 3 *N* HCl and one 40-ml portion of H_2O. After the organic layer was dried ($CaSO_4$) and concentrated, the 9 g (100%) of residue was dissolved in 30 ml of glacial HOAc and 8.5 g of zinc powder was added. The mix-

(33) M. G. Reinecke and L. R. Kray, *J. Org. Chem.*, **29**, 1736 (1964).
(34) N. J. Leonard and A. S. Hay, *J. Amer. Chem. Soc.*, **78**, 1984 (1956).
(35) F. Haase and R. Wolffenstein, *Chem. Ber.*, **37**, 3232 (1904).

ture was stirred at room temperature for 4 hr, filtered to remove the zinc, basified with dilute NaOH, and extracted with three 50-ml portions of ether. The dried (K_2CO_3) ether extract was concentrated to give 3.3 g (76%) of **17** as a dark, viscous liquid which gave two overlapping peaks (48:52) on vpc analysis on a 7 ft, 20% SE-54 on Chromosorb W column. A vpc-collected sample of the mixture had ir 3370, 3100–3000, 1650, 1600, 735, and 700 cm^{-1}; nmr δ 7.1 (s, 5, PhH), 5.4 (two t's, 1, C=CH), 2.3 (two d's, 2, CH_2Ph).

Anal. Calcd for $C_{16}H_{23}N$ (**17**): C, 83.78; H, 10.11; N, 6.11. Found: C, 83.80; H, 10.23; N, 6.13.

N-Methylation of 17 to 14.—A 1.0-g sample of **17** (mixture) was formylated and reduced by the same procedure described for the conversion of **11** to **4** to give 0.8 g (76% yield) of **14** as a vpc-pure liquid whose ir spectrum was identical with that of an authentic sample.[5]

N-Debenzylation of 8 with 2,2,2-Trichloroethyl Chloroformate.—A 3.5-g sample of crude **8** containing 14% of an impurity (**9**) from its preparation from **3** described previously was treated with Cl_3CCH_2OCOCl and then zinc (as for the conversion of **12** to **17**) to give 1.7 g (77%) of a liquid which gave two peaks (87:13) on vpc analysis. The major product was identified as **11** and the minor one as **10** by comparison of their ir spectra with those of previously synthesized samples.

Reaction of 9-Vinylindolizidine (3) with Ethyl Chloroformate. A. Followed by $LiAlH_4$ Reduction.—A solution of 0.9 g of **3**[5] and 11.4 g of ClCOOEt in 50 ml of benzene which had been heated under reflux for 19 hr was washed with 20 ml of 4 *N* HCl and 20 ml of H_2O. The benzene solution was dried (K_2CO_3) and concentrated at reduced pressure to give 1.6 g of a liquid which was heated under reflux with 1 g of $LiAlH_4$ in 50 ml of THF for 15 hr. After excess $LiAlH_4$ had been destroyed with H_2O the mixture was filtered and the filtrate was dried (K_2CO_3) and concentrated to give 0.5 g of a liquid which gave two product peaks in the vpc (column A) in a ratio of 60:40. An ir spectrum of a vpc-collected sample of the minor product was identical with that of **4**,[5] while that of the major product had peaks at 3100, 1630, 1600, and 885 cm^{-1} consistent[36] with that of a conjugated diene.

B. Followed by Catalytic Reduction and Hydrolysis.—A solution of 4.3 g of **3**[5] in 25 ml of benzene was added over a period of 30 min to a solution of 4.1 g of ClCOOEt in 50 ml of benzene and the resulting dark-yellow solution was heated at reflux for 10 hr. The cooled reaction mixture was successively washed with 30 ml of H_2O, two 15-ml portions of 4 *N* HCl, and 15 ml of H_2O and then dried (K_2CO_3) and concentrated at reduced pressure. The residue was passed through a short Al_2O_3 column to give 2.2 g of a liquid whose vpc (column A) had two overlapping peaks. An ir spectrum of this material indicated the presence of unsaturation (3090, 1630, 1600 cm^{-1}) and the nmr spectrum clearly showed the presence of two overlapping ethyl groups, δ 4.1 (q, J = 7 Hz), 1.25 (t, J = 7 Hz).

A solution of 2.1 g of the above mixture in 50 ml of glacial HOAc and 1 g of 10% Pd/C was hydrogenated at 50 psi for 23 hr. The catalyst was removed by filtration and washed with 20 ml of glacial HOAc and the filtrate was basified with concentrated NaOH and extracted with three 50-ml portions of ether. The combined ether extracts were dried (K_2CO_3) and concentrated to give 1.6 g of a liquid whose vpc (column A) contained only one slightly distorted peak.

A solution of the above liquid in 20 ml of glacial HOAc containing 1 g of $TsOH \cdot H_2O$ was heated under reflux for 5 days. The reaction mixture was concentrated at reduced pressure and 35 ml of H_2O and 50 ml of ether were added. The aqueous layer was basified with concentrated NaOH, saturated with K_2CO_3, and extracted with three 30-ml portions of ether. The combined ether extracts were dried (K_2CO_3) and concentrated at reduced pressure to give 0.6 g of a liquid displaying two vpc peaks in a 84:16 area ratio. The minor peak had the same retention time as **20** (*vide infra*) and the major peak was identified as 5-ethylazacyclononane (**19**): micro bp 190–192°; ir 3350 cm^{-1}; nmr δ 2.7 (m, 4, CH_2N).

Anal. Calcd for $C_{10}H_{21}N$ (**19**): C, 77.35; H, 13.63; N, 9.02. Found: C, 77.22; H, 13.65; N, 8.95.

Neither a satisfactory picrate nor a styphnate could be prepared.

Methylation of 5-Ethylazacyclononane (19).—After a solution of 0.3 g of **19**, 2 g of paraformaldehyde, and 0.2 g of *p*-$TsOH \cdot H_2O$ in 10 ml of 88% HCOOH had been heated under reflux for 18 hr, it was washed with 20 ml of ether, basified with dilute NaOH, and extracted with two 30-ml portions of ether. The combined ether extracts were dried (K_2CO_3) and concentrated at reduced pressure to give 0.15 g (46%) of **21** identified by comparison of its ir spectrum with that of an authentic sample.[5]

9-Ethylindolizidine (20). A. From 2.—A solution of 14.2 g of **2** in 50 ml of THF was added to 300 ml of THF containing ethylmagnesium bromide prepared from 21.8 g of ethyl bromide and 8.1 g of magnesium. After refluxing for 4 hr the reaction mixture was decomposed with 200 ml of concentrated NH_4Cl solution and the organic layer was extracted with two 40-ml portions of 6 *N* HCl. The combined acid extracts were saturated with NaCl, washed with benzene, basified with concentrated NaOH, and extracted with three 50-ml portions of ether. The ether extracts were combined, dried (K_2CO_3), and concentrated to yield 5.1 g (35%) of a vpc-pure liquid: bp 38.5° (0.2 mm); ir no unsaturation; nmr δ 2.75 (m, 4, CH_2N), 2.45 (m, 12, CH_2), 0.8 (t, J = 7 Hz, 3, CH_3). A picrate was prepared, mp 236–238° dec (evacuated capillary).

Anal. Calcd for $C_{16}H_{22}N_4O_7$ (**20** picrate): C, 50.26; H, 5.80; N, 14.65. Found: C, 50.16; H, 5.73; N, 14.90.

B. From 3.—A solution of 2.2 g of **3**[5] in 30 ml of glacial HOAc containing 0.3 g of 10% Pd/C was hydrogenated at 40 psi for 24 hr. The catalyst was removed by filtration and the solvent by evaporation at reduced pressure to leave a residue which was taken up in concentrated NaOH and extracted with three 25-ml portions of ether. The combined ether extracts were dried (K_2CO_3) and concentrated to leave 1.65 g (75%) of an oil containing one major peak and two trace constituents in the vpc. The ir spectrum of a vpc-collected sample of the former was identical with that of **20** prepared above.

Reaction of 9-Vinylindolizidine (3) with Phenyl Chloroformate.—A mixture of 3.6 g of **3**,[5] 4.0 g of PhOCOCl, and 2.0 g of K_2CO_3 in 65 ml of ether was heated to reflux for 15 min, 3 ml of H_2O was added, and heating was continued for another 50 min. Another 10 ml of H_2O was added, the layers were separated, and the ether layer was washed with two 20-ml portions of 3 *N* HCl and one 20-ml portion of H_2O. The ether was dried (K_2CO_3) and concentrated and the residue was chromatographed on a short column of activity I Al_2O_3 with *n*-hexane–benzene. Evaporation of the eluate left 3.3 g of a viscous liquid: ir 3100, 3000, 1715, 1630, 1600, 750, 675 cm^{-1}; nmr δ 7.1, 6.5–4.7, 3.2, 2.6–1.2 (all m).

A mixture of 2.5 g of the above oil, 1 g of 10% Pd/C, and 50 ml of glacial HOAc was hydrogenated for 20 hr at room temperature and atmospheric pressure. The catalyst was removed by filtration, the solvent by evaporation, and the residue was taken up in 50 ml of ether. The ether was washed with two 20-ml portions of 3 *N* HCl, one 10-ml portion of H_2O, and one 20-ml portion of dilute NaOH. The dried (K_2CO_3) ether solution was evaporated to leave 1.6 g of a liquid: ir 3060, 3040, 1720, 1595, 750, 680 cm^{-1}; nmr δ 7.1, 3.4, 1.4 (all m). Acid hydrolysis of this liquid by the same procedure used for the ethyl carbamate of **19** yielded 0.5 g of a liquid whose major constituent (89%) by vpc on column B was identified as **19** by comparison of its ir spectrum with that of an authentic sample from the EtOCOCl cleavage.

Reaction of 9-Benzylindolizidine (22) with Phenyl Chloroformate.—After a mixture of 6.0 g of **22**[4] and 2.3 g of PhOCOCl in 50 ml of ether had been allowed to react for 14 hr at room temperature, it was washed with two 30-ml portions of 3 *N* HCl and three 30-ml portions of dilute NaOH. Evaporation of the dried (K_2CO_3) ether extracts left 3.3 g of a viscous oil: ir 3060, 3030, 1725, 1630, 1600, 750, 690, 680 cm^{-1}; nmr δ 7.1 (s, PhH), 6.3 (C=CHPh), 5.2 (C=CH), 3.2, 1.9 (all m).

Reduction of a 1-g portion of this oil with $LiAlH_4$ according to the procedure used for the ethyl chloroformate of **3** gave 0.5 g of a liquid whose vpc analysis on column A gave two peaks (70:30) neither of which had the same retention time as **22**.

Another 3.1 g of the oily carbamate mixture was heated to reflux with 2 g of NaOH in 45 ml of EtOH for 16 hr. The solvent was removed at reduced pressure and the residue was taken up in 50 ml of H_2O and extracted with two 50-ml portions of ether. The combined ether extracts were extracted with two 30-ml portions of 4 *N* HCl which were then combined, basified with concentrated NaOH, and extracted with three 30-ml portions of ether. Evaporation of the combined and dried (K_2CO_3) extracts left 0.9 g of a liquid whose vpc displayed one major peak (>99%) which was identified as **22** by comparison of its ir spectrum with that of an authentic sample.

(36) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 40.

1-Phenyl-2-dimethylamino-2-methylpropane (26).—A mixture of 10 g of α,α-dimethylphenethylamine,[37] 5 g of paraformaldehyde, 10 ml of 88% HCOOH, and 0.3 g of *p*-TsOH in 15 ml of H_2O was heated under reflux for 19 hr. The cooled mixture was basified with concentrated NaOH and extracted with two 50-ml portions of ether and the dried (K_2CO_3) ether layers were evaporated at reduced pressure to give 10.3 g (86%) of vpc-pure **26**: micro bp 235°; nmr δ 7.1 (s, 5, ArH), 2.6 (s, 2, CH_2), 2.2 (s, 6, NCH_3), 0.9 (s, 6, CCH_3). A picrate, mp 193–193.5°, was prepared.

Anal. Calcd for $C_{18}H_{22}N_4O_7$ (**26** picrate): C, 53.19; H, 5.45; N, 13.78. Found C, 52.99; H, 5.70; N, 13.73.

Reaction of 26 with Phenyl Chloroformate.—A stirred mixture of 832 mg of **26** and 1.46 g of phenyl chloroformate in 30 ml of ether (white percipitate) was allowed to react at room temperature for 2.5 hr, at which time 350 mg of K_2CO_3 was added. After 14 hr a drop of H_2O was added, and the mixture was stirred for 2.5 hr more and then filtered. The filtrate was washed with two 5-ml portions of 5% HCl and three 5-ml portions of 5% KOH. The dried (K_2CO_3) ether layer was concentrated to give 1.29 g of a clear liquid whose vpc (4.5 ft × 0.25 in., 20% SE-30 on Chromosorb P) contained five peaks, the first two of which (*ca.* 1:1) corresponded to methylallylbenzene and α,α-dimethylsytrene in order of increasing retention time. Positive identification was made by a comparison of the vpc retention times, nmr spectra, and mass spectra (Finnegan Model 1015 SL instrument at 70 eV) with those of authentic samples.[37]

Reaction of 9-Vinylindolizidine (3) with $LiAlH_4$ and $NiCl_2$.—To a stirred solution of 7.6 g of $LiAlH_4$ in 500 ml of THF was slowly added 8.0 g of anhydrous $NiCl_2$ and the resulting mixture was heated to reflux for 30 min, at which time 4.0 g of **3**[5] was introduced. After being refluxed for an additional 16 hr, the reaction mixture was cooled, the excess $LiAlH_4$ was destroyed with methanol, 200 ml of ether was added, and the mixture was heated to reflux for another hour. The cooled mixture was filtered, H_2O was added to the filtrate until precipitation was complete, and the mixture was filtered again. This filtrate, including the ether washings of the precipitates, was extracted with three 30-ml portions of 4 *N* HCl and the combined extracts were saturated with KCl and washed with two 50-ml portions of ether which were then combined, dried (K_2CO_3), and concentrated to give 3 g (~75%) of a yellow oil. Vpc analysis (column B) showed four peaks in addition to unreacted starting material (**3**) and a trace of indolizidine. The products of lowest and highest retention time were identified as 9-ethylindolizidine (**20**) and 5-ethylideneazacyclononane (**11**) by comparison of their ir spectra with those of authentic samples. The remaining two products, whose vpc peaks were not completely resolved, were provisionally identified as 5-ethylazacyclononane (**19**) and 5-vinylazacyclononane (**10**) in order of increasing retention time by, in the first case, spiking with an authentic sample and in the second instance by the spectral characteristics: ir 3350 (NH), 3075 (C=CH), 1625 (C=C), and 900 cm^{-1} ($CH=CH_2$); nmr δ 5.75 (m, 1, HC=C), 4.8 (m, 2, $C=CH_2$), 2.75 (m, 5, CH_2N and NH or CHC=).

Selected variations from the above conditions and product analyses are given in Table I.

N-Methylation of Product from Above Reaction of 3.—The 3 g of product from reaction 7 in Table I was dissolved in 2 ml of formic acid and cooled, and the cooled acetic–formic anhydride mixture previously prepared[38] from 4 ml of formic acid and 8 ml of Ac_2O was added. After sitting for 2 hr at room temperature the solution was treated with ice, basified with concentrated NaOH, and extracted with three 20-ml portions of ether. The combined ether layers were washed with two 20-ml portions of 3 *N* HCl and one 20-ml portion of H_2O, dried over K_2CO_3, and concentrated to give 0.7 g of a neutral liquid.

A stirred mixture of 0.6 g of this liquid and 0.5 g of $LiAlH_4$ in 40 ml of ether and 5 ml of THF was heated at reflux for 21 hr. The excess $LiAlH_4$ was decomposed with H_2O, the mixture was filtered, and the filtrate and ether washings of the precipitate were combined, dried (K_2CO_3), and concentrated to give 0.6 g of a light yellow oil. Vpc analysis of this oil on a 15 ft, 5% KOH, 15% PPE on Chromosorb W column gave three peaks in an area ratio of 15:42:43 which were identified as the *N*-methylamines **21**, **29**, and **4**, respectively, from a comparison of the ir spectra of vpc-collected material with those of authentic samples.[5] The vpc-area ratio of the secondary amines **19**, **10**, and **11** in the reactant was 14:42:44. Similar experiments with mixtures of **19**, **10**, and **11** of different composition also gave mixtures of **21**, **29**, and **4** with unchanged compositions.

Acknowledgment.—This research was generously supported by The Robert A. Welch Foundation, the National Science Foundation,[2] and the TCU Research Foundation.

Registry No.—**2**, 30820-52-1; **3**, 35201-24-2; **4**, 35249-63-9; **5**, 40952-29-2; **6**, 40952-30-5; **8**, 40952-31-6; **8** benzyl bromide salt, 40952-32-7; **11**, 40952-33-8; **11** styphnate, 40952-34-9; **12**, 40952-35-0; **12** methiodide, 40952-36-1; **13**, 40952-37-2; **14**, 40952-38-3; **16**, 40952-39-4; **17**, 40952-40-7; **19**, 40952-41-8; **20**, 40952-42-9; **20** picrate, 40952-43-0; **21**, 40952-44-1; **22**, 4753-49-5; **26**, 40952-46-3; **26** picrate, 40952-47-4; indolizidine, 13618-93-4; NaCN, 143-33-9; ethyl chloroformate, 541-41-3; $PhCH_2Br$, 100-39-0; PhOCOCl, 1885-14-9; *N*-benzylpieripdine, 2905-56-8; 2,2,2-trichloroethyl chloroformate, 17341-93-4; α,α-dimethylphenethylamine, 122-09-8.

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The Structure and Chemistry of the Aldehyde Ammonias. 1-Amino-1-alkanols, 2,4,6-Trialkyl-1,3,5-hexahydrotriazines, and *N,N'*-Dialkylidene-1,1-diaminoalkanes[1]

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Received April 10, 1973

Reaction of aliphatic aldehydes with 15 *M* aqueous ammonia at −10 ± 15° leads instantly to very unstable, low-melting solids believed to be principally 1-amino-1-alkanol hydrates (**1a–i**). On standing in 15 *M* aqueous ammonia at 0–5° these solids are converted to 2,4,6-trialkyl-1,3,5-hexahydrotriazines (**2a–h**), usually isolated as their low-melting crystalline hydrates. Some of these triazine hydrates are the "aldehyde ammonias" prepared and described by earlier workers. Anhydrous triazines **2a–h** have been prepared; their nmr spectra and chemical behavior indicate all-equatorial 2,4,6-trialkyl substitution. Their oxidation with *tert*-butyl hypochlorite leads to 2,4,6-trialkyl-1,3,5-triazabicyclo[3.1.0]hexanes. On warming above 25° they lose ammonia rapidly to form *N,N'*-dialkylidene-1,1-diaminoalkanes (**10**); aldimines, RCH=NH, are not obtained. Pivaldehyde and 2-ethylbutanal react with 15 *M* aqueous ammonia to yield *N,N'*-dialkylidene-1,1-diaminoalkanes **10d** and **10e** and do not form stable 2,4,6-trialkyl-1,3,5-hexahydrotriazines.

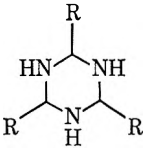
Reaction of aliphatic aldehydes with ammonia leads to the "aldehyde ammonias." The first reported, acetaldehyde ammonia, was discovered by Liebig in 1835.[3a] Preparations of many of these materials are described in the early literature (reaction temperature 0 ± 15°).[3] The substances are often isolated as colorless, unstable, low-melting solids. Considerable confusion exists regarding their structures, which, with the exception of acetaldehyde ammonia, have not been established. Most frequently they are formulated as 1-amino-1-alkanols, $RCH(OH)NH_2$.[4-7] It has been shown in the present work that most of the "aldehyde ammonias" isolated and described by previous workers are 2,4,6-trialkyl-1,3,5-hexahydrotriazines or hydrates thereof.

1-Amino-1-alkanols—Aldehyde ammonias believed to be hydrates of the elusive and fugitive 1-amino-1-alkanols, precursors to the 2,4,6-tialkyl-1,3,5-hexahydrotriazines, have been prepared (**1a–i**, Table I). These were obtained by addition of aliphatic aldehydes to cold concentrated (15 *M*) aqueous ammonium hydroxide (−10 ± 15°; 5–10 min). Precipitation of the isolated products occurs instantly. Rapid filtration through a cold funnel affords white solids melting near room temperature. The nitrogen and water assays indicate the substances to be hydrates having a 1:1 ratio of aldehyde to ammonia.

$$RCHO + NH_3(aq) \rightleftharpoons \underset{\mathbf{1}}{RCH(OH)NH_2 \cdot xH_2O}$$

The materials tentatively designated 1-amino-1-alkanol hydrates **1a–i** (aldehyde ammonia hydrates) are very unstable materials, much less stable than the 2,4,6-trialkyl-1,3,5-hexahydrotriazines (*vide infra*). They readily evolve ammonia on standing. Their infrared spectra, measured at 25°, reveal aldehyde carbonyl and imine C=N bands indicating rapid dehydration and deamination; this decomposition process is slower with higher melting **1d** and **1f**. Stability and other properties vary with the alkyl substituent. Stabilities increase, and aqueous solubilities decrease, as the alkyl group increases in carbon content. Addition of isobutyraldehyde or 2-ethylbutanal to 15 *M* aqueous ammonia at −25° produced no solid; the substances formed initially are liquids at this temperature.

Conversion of **1a–i** (except **1f** from pivaldehyde) to 2,4,6-trialkyl-1,3,5-hexahydrotriazines (**2**) occurs



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rapidly in pyridine-d_5, as shown by examination of nmr spectra. These spectra reveal virtually no aldehyde or olefinic methine proton signals and are essentially spectra of pure **2**, indicating rapid formation of cyclic triazines in pyridine solution. In aqueous ammonia at 0° the aldehyde ammonia hydrates **1c**, **1d**, **1g**, and **1h** are observed to melt within 2 hr, forming a floating layer which more slowly changes to the corresponding crystalline triazine or hydrate thereof.

Structures other than 1-amino-1-alkanols might be considered for the products described in Table I. The observed 1:1 ratio of aldehyde to ammonia in these substances precludes dicarbinolamines, $(RCHOH)_2NH$, and tricarbinolamines, $(RCHOH)_3N$. The principal reason for excluding diamines, $RCHOHNHCH(R)NH_2$, and acyclic or epimeric cyclic triamines is that under the reaction conditions described rates of formation of dimers and trimers are expected to be very much slower than the rate of formation of **1**.

(1) Presented in part at the Fourth International Congress of Heterocyclic Chemistry, Salt Lake City, Utah, July 1973.

(2) National Research Council Postdoctoral Research Associate, 1971–1973.

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TABLE I
PROPERTIES OF ALDEHYDE AMMONIA HYDRATES

Compd[a]	R	Mp, °C	Yield, %	Molecular formula[b]	Nitrogen, % Calcd	Nitrogen, % Found
1a	CH_3	25–28	3	$C_2H_7NO \cdot 2H_2O$	14.73	15.3
1b	C_2H_5	15–18	39	$C_3H_9NO \cdot 3H_2O$	10.85	11.3
1c	n-C_3H_7	20–22	38	$C_4H_{11}NO \cdot 3H_2O$	9.78	9.4
1d	n-C_4H_9	38–42	100	$C_5H_{13}NO \cdot 3H_2O$	8.91	8.9
1e	i-C_4H_9	25–26	63	$C_5H_{13}NO \cdot 3H_2O$	8.91	8.9
1f	t-C_4H_9	38–40	59	$C_5H_{13}NO \cdot 3H_2O$	8.91	8.8
1g	n-C_5H_{11}	15–20	55	$C_6H_{15}NO \cdot 3H_2O$	8.17	7.9
1h	n-C_6H_{13}	12–15	100	$C_7H_{17}NO \cdot 3H_2O$	7.56	7.9
1i	n-$C_{11}H_{23}$	38–42	100	$C_{12}H_{27}NO \cdot 4H_2O$	5.12	4.9

[a] Tentative structure assignment. [b] Tentative assignment based on nmr spectra and nitrogen and water assays.

This would be particularly true for the higher homologs. For example, the formation of 2,4,6-trihexyl-1,3,5-hexahydrotriazine from heptanal in aqueous ammonia in 68% yield requires a reaction time of 3 months at 0°, whereas the aldehyde ammonia hydrate **1h** is formed instantly in quantitative yield under the same conditions. Dodecanal would be expected to react even more slowly to form a dimer or trimer. Pivaldehyde, which does not produce a cyclic triazine (**2**), forms **1f** instantly. Cyclic triazines (**2**) evolve virtually no ammonia at 0° and show no infrared carbonyl band, as expected. On the other hand, 1-amino-1-alkanols could evolve ammonia rapidly at 0° and produce the observed carbonyl bands by facile retrogression to aldehyde by deamination.

The aldehyde ammonias listed in Table I appear not to have been isolated or described as such by others. Waage noted the transient formation of a white precipitate (not isolated) when ammonia was passed into a cold (*ca.* −15°) solution of propanal in petroleum ether (bp 35–100°); the precipitate liquefied on warming.[3b] In aqueous ammonia, acetaldehyde and propionaldehyde produce no precipitate at 0°; a lower temperature (−25°) is required to produce **1a** and **1b**. Butanal and isovaleraldehyde have been studied often in reactions with ammonia.[3c,e,h,4] In aqueous ammonia they form an initial white precipitate (**1c**, **1e**), but it is replaced rather rapidly by a second white precipitate of essentially identical appearance (isolated triazine polyhydrates). Heptanal has been reported to react with ammonia to produce oils.[3g,k] A known chloral ammonia, mp 62–63°, may be 2,2,2-trichloro-1-aminoethanol.[5,7-9] A few substances described as dicarbinolamines, $(RCHOH)_2NH$, have been reported, prepared at −20° by reaction of an *excess* of aldehyde with ammonia: R = CCl_3,[8,9] C_6H_5,[10] 4-$CH_3C_6H_4$.[10] Carbinolamines derived from aldehydes and ammonia, or amines, are generally quite unstable substances which may be isolated at low temperatures only in a few favorable instances.[7-15]

2,4,6-Trialkyl-1,3,5-hexahydrotriazines.—The "aldehyde ammonias" prepared by earlier workers[3,4,9] by reactions of aliphatic aldehydes with ammonia were assigned various structures. Linear monomeric, dimeric, trimeric, and polymeric carbinolamine type structures have been proposed.[3d,e,16,17] Delépine was first to suggest that acetaldehyde ammonia is 2,4,6-trimethyl-1,3,5-hexahydrotriazine trihydrate.[18] This structure was later confirmed by X-ray crystallographic studies.[19,20] No X-ray studies have been made of other aldehyde ammonias and results of attempts to elucidate their structures by chemical methods have been inconclusive.[17] A few authors have suggested that the known homologous aldehyde ammonias are 2,4,6-trialkyl-1,3,5-hexahydrotriazines.[18,21] Most frequently, however, one finds all of these substances (even acetaldehyde ammonia) described as 1-amino-1-alkanols.[3-7,22,23] Much of the earlier confusion arose because of the variable degree of hydration exhibited by these materials, and their instability. We have now prepared pure anhydrous and hydrated forms of the known aldehyde ammonias and have shown by molecular weight determinations, spectral data, and chemical behavior that they are 2,4,6-trialkyl-1,3,5-hexahydrotriazines or hydrates thereof (**2a–h**·xH_2O, R = alkyl; Table II).

Certain aldehydes having electronegative substituents have been reported to yield 2,4,6-trisubstituted 3,5-hexahydrotriazines by reaction with ammonia—compound, R: **2i**, CH_2Br;[11] **2j**, CCl_3;[5,8,9,24,25] **2k**, CF_3;[26] **2l**, CH_2OCH_3;[27] **2m**, $CH_2OC_2H_5$;[27] **2n**, 2-pyridyl;[28] **2o**, 2-(3,4-dihydro-2*H*-pyranyl).[29] Formaldehyde and ammonia are reported to react in aqueous solution to

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TABLE II

2,4,6-TRIALKYL-1,3,5-HEXAHYDROTRIAZINES AND HYDRATES

Compd	R	Yield, %[a]	Mp, °C	Molecular formula	Calcd, % C	H	N	Mol wt	Found, % C	H	N	Mol wt[b]
2a	CH_3		94–96[c]	$C_6H_{15}N_3$	55.77	11.70	32.53	129.20	55.30[d]	11.50[d]	32.21[d]	129
		75	94–95[e]	$C_6H_{15}N_3 \cdot 3H_2O$	39.33	11.55	22.93		39.34[f]	11.48[f]	22.95[f]	
2b	C_2H_5	89	2–3	$C_9H_{21}N_3$	63.11	12.36	24.53	171.28	63.08	12.49	24.20	180
			13–15	$C_9H_{21}N_3 \cdot 3H_2O$			18.64				18.1[g]	
2c	n-C_3H_7		6–8	$C_{12}N_{27}N_3$	67.55	12.76	19.70	213.36	67.65	12.51	19.1[g]	221
		67	28–30[h]	$C_{12}H_{27}N_3 \cdot 18H_2O$	26.81	11.81	7.82		26.74[i]	11.84[i]	7.81[i]	
2d	i-C_3H_7	78	26–27[j]	$C_{12}H_{27}N_3$	67.55	12.76	19.70	213.36	67.70	12.68	19.60	224
2e	n-C_4H_9		Oil	$C_{15}H_{33}N_3$	70.53	13.02	16.45	255.44	70.35	12.86	16.10	245
		82	16–17	$C_{15}H_{33}N_3 \cdot 3H_2O$			13.57				13.7[g]	
2f	i-C_4H_9		21–23[k]	$C_{15}H_{33}N_3$			16.45	255.44			15.5[g,k]	269
		92	59–60[l]	$C_{15}H_{33}N_3 \cdot 24H_2O$	26.19	11.87	6.11		26.2[m]	11.8[m]	6.2[g,m]	
2g	n-C_5H_{11}		−9 to −7	$C_{18}H_{39}N_3$	72.66	13.22	14.12	297.52	72.90	13.33	14.08	295
		56	15–17	$C_{18}H_{39}N_3 \cdot 3H_2O$			11.92				12.08	
2h	n-C_6H_{13}		−6 to −5	$C_{21}H_{45}N_3$	74.27	13.36	12.37	339.59	74.38	13.33	12.26	262[n]
		68	13–15	$C_{21}H_{45}N_3 \cdot 3H_2O$			10.67				10.6[g]	

[a] Yield of isolated form. [b] Determined by vapor osmometry in chloroform solvent except for **1a** (mass spectroscopy). [c] Lit. mp 95°, ref 9, 16, 18b. [d] Data of Delépine, ref 18b. [e] Lit. mp 85°,[3a] 92–93°,[4] 95°,[16] 96–98°.[9] [f] Data of Aschan, ref 9. [g] Nitrogen determination by titration of freshly prepared sample, this laboratory. [h] Lit.[4] mp 25.5–26°, 63% yield; mp 30–31°.[3d] [i] Data of Guckelberger, ref 3c. [j] Lit.[3e] mp 31°. [k] Sample contains *ca.* 20% diimine **10** (R = i-C_4H_9, $C_{15}H_{30}N_2$); see Experimental Section. [l] Lit.[3b] mp 56–58°. [m] Data of Strecker, ref 3f. [n] Partial decomposition of the sample occurs in solution at 25°.

form principally the parent 1,3,5-hexahydrotriazine (**2p**, R = H).[30–33]

Several procedures for preparation of 2,4,6-trialkyl-1,3,5-hexahydrotriazines (**2**) were examined in the present work. The most simple, effective, and general one is to add the aldehyde to 4 molar equiv of concentrated (15 *M*) aqueous ammonia at 5–10°, followed by storage at 0–5° for several days or weeks. The "aldehyde ammonias" described in the earlier literature were prepared by addition of the aldehyde to excess ice-cold concentrated ammonia, or by passing ammonia gas into the aldehyde or a solution of the aldehyde (cold) in an inert solvent such as ether. Reaction in liquid ammonia has been reported.[17] Reported procedures which employed other than aqueous ammonia often gave nitrogen-containing oils of somewhat indefinite molecular formula.[3b,g,j,k,16,17]

Two properties of the known aldehyde ammonias confused earlier attempts at structure elucidation. One is their instability causing loss of ammonia at ambient temperature; stability decreases with increasing carbon content. The other concerns the variable composition of their hydrates and the failure to recognize some of the products as hydrates. Except for acetaldehyde ammonia, earlier attempts to prepare the anhydrous compounds led to their decomposition.

Butanal and isovaleraldehyde are exceptional in forming triazine hydrates containing 18 and 24 water molecules, respectively. Triazine **2f** when added to water produces a striking effect. The hydrate forms instantly as a slightly soluble white precipitate containing water as "open ice" equal in weight to nearly twice that of the reacting triazine; on melting its water is released as a lower layer. Triazine **2c** behaves similarly. Because of the instability of these triazines this process cannot be repeated indefinitely. The water in crystalline 2,4,6-trimethyl-1,3,5-hexahydrotriazine is located in a cavity containing six water molecules.[20] In the hydrates of **2c** and **2f** the cavity must be quite large and could accommodate up to 46 water molecules.[34] Clathrate hydrates of simple amines are known.[35]

The anhydrous 2,4,6-trialkyl-1,3,5-hexahydrotriazines **2a–h** (except **2b** and **2d**) were prepared from their hydrates by several dehydration procedures. They were isolated as oils which crystallized on chilling. Further purification of some could be achieved by crystallization from isopentane at low temperature. The nmr spectra of anhydrous triazines **2a–h** in pyridine-d_5 were virtually identical with those of the corresponding hydrated forms, except for the absence of a water line and some slight chemical shifts caused by a change in solvent polarity. The anhydrous triazines, with the exception of the trimethyl compound **2a**, have melting points lower than those of the corresponding hydrates. On addition of water they reform the original hydrates. The triazines **2a–h** and their hydrates are stable as white, crystalline solids for at least several months when stored at −15°. At room temperature the anhydrous compounds are hygroscopic liquids (except **2a**) which react with the moisture and carbon dioxide of the air and slowly evolve ammonia.

Structures of the anhydrous triazines **2a–h** were established by determination of molecular weight, elemental analyses, spectra, and chemical behavior. Infrared spectra of pure samples revealed NH bands at *ca.* 3200 and 3350 cm^{-1}; no bands appeared in the double bond stretching region, indicating absence of C=C, C=O, and C=N bonds. The nmr spectra in pyridine-d_5 revealed three ring methine protons (δ 3.6–4.1) and three NH protons, usually a broad signal at δ 1–2 hidden by the alkyl proton signal; addition

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TABLE III

PROTON NMR SPECTRA OF ANHYDROUS 2,4,6-TRIALKYL-1,3,5-HEXAHYDROTRIAZINES. δ VALUES IN PYRIDINE-d_5 AT 30° (TETRAMETHYLSILANE INTERNAL STANDARD)

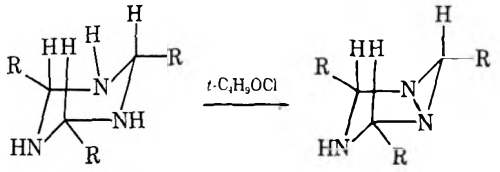
		Nmr signals, δ[a]		
Compd	Alkyl R	Ring CH	Alkyl CH, CH_2	Alkyl CH_3
2a	CH_3	3.87 q ($J \cong 6$ Hz)		1.24 d ($J \cong 6$ Hz)
2b	C_2H_5	3.64 t[b]	CH_2, 1.2–1.9 m	1.01 t[c]
2c	n-C_3H_7	3.70 t[b]	$(CH_2)_2$, 1.2–2.0 m	0.87 t[c]
2d	i-C_3H_7	3.67 d ($J \cong 6$ Hz)	CH, 1.4–2.0 m	1.18 d ($J \cong 6$ Hz)
2e	n-C_4H_9	3.96 t[b]	$(CH_2)_3$, 1.0–2.0 m	0.92 t[c]
2f	i-C_4H_9	4.14 t ($J \cong 7$ Hz)	CH, 1.7–2.5 m CH_2, 1.5–1.9 m	0.98 d ($J \cong 7$ Hz)
2g	n-C_5H_{11}	3.93 t[b]	$(CH_2)_4$, 1.0–2.0 m	0.88 t[c]
2h	n-C_6H_{13}	3.63 t[b]	$(CH_2)_5$, 1.0–2.0 m	0.83 t[c]

[a] A broad NH signal occurs at *ca.* δ 1–2 in compounds **2a–h**. Addition of D_2O produces an OH signal at δ 5.5 ± 0.5 corresponding in intensity to three exchangeable protons. [b] An apparent triplet signal which is sharpened on addition of D_2O ($J \cong 6$ Hz). These signals are broader for solutions of compounds **2e–h** containing no added D_2O. [c] An apparent triplet signal ($J \cong 6$ Hz).

of D_2O showed three readily exchangeable protons and produced a sharpening of the ring methine proton signal (Table III).

The stereochemistry of triazines **2a–h** is indicated by their relatively simple nmr spectra. In **2a**, **2b**, and **2d** sharp, clearly resolved signals are observed for ring methine and alkyl protons, indicating only one epimer having all alkyl groups equatorial. Although the spectra of **2c** and **2e–h** are not completely resolved in the alkyl region, their larger alkyl groups would also be expected to be all equatorial. These conclusions are in agreement with ^{13}C nmr spectra (to be published) and the structure of **2a** determined by X-ray crystallography.[20] In related 2,4,6-trimethyl-1,3,5-hexahydrotrioxane the all-equatorial configuration of methyl groups is favored.[36]

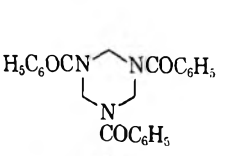
Additional evidence establishing the stereochemistry and structure of the triazines **2a–h** was obtained by their oxidation with *tert*-butyl hypochlorite in methanol (1 equiv of sodium carbonate added) at −40° to produce 2,4,6-trialkyl-1,3,5-triazabicyclo[3.1.0]hexanes **3a–h**. The triazine hydrates gave the same products. Products having cis stereochemistry of the C-2, C-4 substituents (**3a–c**) were obtained with reactants hav-



2a–c → *cis*-**3a**, R = CH_3; *cis*-**3b**, R = C_2H_5; *cis*-**3c**, R = n-C_3H_7

ing relatively small R groups (**2a–c**, R = CH_3, C_2H_5, n-C_3H_7). Reactants having alkyl groups larger than n-C_3H_7 produced triazabicyclo[3.1.0]hexanes **3e–h** having C-2, C-4 trans stereochemistry only. These results and an alternate synthesis of **3** are discussed in detail elsewhere.[37–39]

Few reactions of the 2,4,6-trialkyl-1,3,5-hexahydrotriazines (other than 2 → **3**) leave the original triazine ring intact. Several N-substituted derivatives of 1,3,5-hexahydrotriazine itself are known and a few of these have been prepared from aqueous solutions believed to contain this compound. For example, benzoyl chloride yields the trisbenzoyl deriative **4** in 13% yield,[30,32] and nitrous acid yields the trinitroso compound **5a** in 52% yield.[32] Although 2,4,6-trimethyl-1,3,5-hexahydrotriazine (**2a**) reacts with nitrous acid to provide a 5% yield of the trinitroso derivative **5b**,[18d,e] reaction with benzoyl chloride under a variety



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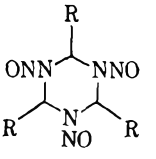
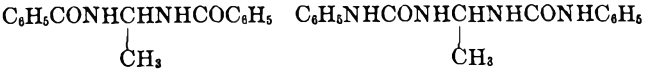


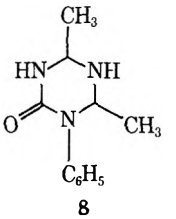
5a, R = H
b, R = CH_3

of conditions failed to yield a 1,3,5-trisbenzoyl derivative of **2a**. The product was *N*,*N*-dibenzoyl-1,1-diaminoethane (**6**), in agreement with earlier findings.[40,41] Reaction of anhydrous **2a** with 1 molar equiv of phenyl isocyanate in tetrahydrofuran gave the bisurea **7** rather than the 1,3,5-triphenylcarbamoyl derivative of **2a**.



6 **7**

Known **7** has been synthesized from acetaldehyde and phenylurea.[42] Phenyl isocyanate has been reported to react with an *excess* of **2a** in ether to form 2,4-dimethyl-6-oxo-1-phenyl-1,3,5-hexahydrotriazine (**8**).[43]



8

The scope and limitations of the reaction of aldehydes with ammonia to yield 2,4,6-trisubstituted 1,3,5-hexahydrotriazines (of sufficient stability to permit

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(39) R. L. Atkins, D. W. Moore, D. Mallory, J. M. La Berge, and A. T. Nielsen, Abstracts, 165th National Meeting of the American Chemical Society, Dallas, Texas, April 1973, Paper No. C-63.
(40) K. Kraut and Y. Schwartz, *Justus Liebigs Ann. Chem.*, **223**, 40 (1884).
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TABLE IV

PROTON NMR SPECTRA OF *N,N'*-DIALKYLIDENE-1,1-DIAMINOALKANES, RCH(N=CHR)$_2$. δ VALUES IN DEUTERIOCHLOROFORM AT 30° (TETRAMETHYLSILANE INTERNAL STANDARD)

		Methine signals		Alkyl signals	
Compd	R	Imino RCH=N	Alkyl CHR	Alkylidene RCH=	Alkyl CHR
10a	CH_3	7.82 (J = 4.5 Hz)[a,b]	4.50 q (J = 6 Hz)[a]	CH_3, 1.98 d (J = 4.5 Hz)[a]	CH_3, 1.37 d (J = 6 Hz)[a]
10b	C_2H_5	7.72 t[b] (J = 4.5 Hz)	4.17 t[c] (J = 6 Hz)	CH_3, 1.10 t (J = 7 Hz) CH_2, 2.2–2.8 m	CH_3, 0.98 t (J = 7 Hz) CH_2, 1.4–2.0 m
10c	*i*-C_3H_7	7.58 d[b] (J = 4.5 Hz)	3.92 d (J = 6 Hz)	CH_3, 1.10 d (J = 7 Hz) CH, 2.2–2.8 m	CH_3, 0.97 d (J = 7 Hz) CH, 1.6–2.2 m
10d (cis,trans)	*t*-C_4H_9	7.52 s[b]	3.83 s[c]	CH_3, 1.09 s	CH_3, 0.90 s
10d (trans,trans)	*t*-C_4H_9	7.52 s[b]	3.83 s[c]	CH_3, 1.09 s	CH_3, 0.88 s
10e	$(C_2H_5)_2CH$	7.50 d[b] (J = 6 Hz)	4.32 d (J = 3.5 Hz)	CH_3, 0.89 t[d] CH_2, 1.2–1.7 m CH, 1.8–2.3 m	CH_3, 0.90 t[d] CH_2, 1.2–1.7 m CH, 1.2–1.8 m[e]

[a] Caprio, *et al.*, report δ 7.6 q (J = 4.5 Hz), 4.3 q (J = 6 Hz), 1.9 d (J = 4.5 Hz), 1.2 d (J = 6 Hz) in carbon tetrachloride (ref 44). [b] Signals split to doublet ($J \cong 1$ Hz). [c] Signals split to triplet ($J \cong 1$ Hz). [d] Apparent triplet, $J \cong 7$ Hz). [e] Signal obscured by the CH_2 signal.

their isolation and storage) may now be defined. With *n*-alkanals the reaction succeeds with all those examined (through heptanal). The reaction is much slower with heptanal than with acetaldehyde, and the heptanal-derived triazine product (**2h**) is less stable than **2a**. These observations agree with the conclusions of Ogata and Kawasaki on the kinetics of the reaction of aldehydes with ammonia: electron-releasing groups were found to decrease the forward rate and increase the reverse rate of the reaction.[4] (These authors did not recognize their products as triazines.) Alkyl-substituted alkanals having substituent in the β–ω positions should undergo the reaction; isovaleraldehyde forms triazine **2f** readily. Electronegatively substituted aldehydes such as chloral react with ammonia easily, forming rather stable substituted hexahydrotriazines.[8,9,11,24–29] Isobutyraldehyde is the only α-branched alkyl-substituted alkanal observed to produce a stable triazine (**2d**). Pivaldehyde and 2-ethylbutanal failed to yield isolable triazines; the products are principally *N,N'*-dialkylidene-1,1-diaminoalkanes. The reaction also fails with aryl carboxaldehydes such as benzaldehyde and furfural, the products being hydrobenzamide types [ArCH(N=CHAr)$_2$].[10,23] A product described as 2,4,6-triphenyl-1,3,5-hexahydrotriazine is believed to be hydrobenzamide.[21]

***N,N'*-Dialkylidene-1,1-diaminoalkanes and Other Products.**—On gentle heating (40–80°) the 2,4,6-trialkyl-1,3,5-hexahydrotriazines **2a–h** readily lose ammonia to produce *N,N'*-dialkylidene-1,1-diaminoalkanes **10** (hydracetamides) in high yield. Nmr spectra sup-

$$\mathbf{2a\text{–}h} \rightleftharpoons \underset{\mathbf{9}}{[RCH(NH_2)NHCH(R)N{=}CHR]} \overset{-NH_3}{\underset{NH_3}{\rightleftharpoons}} RCH(N{=}CHR)_2 \quad \mathbf{10}$$

port the assigned structures (Table IV). The reaction is reversible. Excess ammonia reacts with the diimines to regenerate the cyclic triazines. These reactions are believed to involve the acyclic triamine intermediate **9**.

Stability of diimines **10** varies with substituent R. The trimethyl compound **10a** (R = CH_3; hydracetamide itself) is a liquid (mp −5°) which polymerizes readily.[44] (Yellow solids, previously referred to as hydracetamide, may contain polymers of **10a**.[17,45,46]) Diimines with small *n*-alkyl groups (**10a, 10b**) polymerize extremely readily on heating. Polymerization during preparation may be diminished by heating the reactant triazine at reflux as a dilute solution (*ca.* 1%) in an inert solvent such as hexane; the triethyl compound **10b** was prepared in this manner in 80% yield. Diimines containing alkyl groups with α branching [*i*-C_3H_7, *t*-C_4H_9, $(C_2H_5)_2CH$, etc.] are rather stable. *N,N'*-Diisobutylidene-1,1-diamino-2-methylpropane (**10c**) was prepared in 87% yield by distillation of the neat triazine **2d** at 12 mm. Several diimines having α-branched R groups, including **10c**, have been reported.[22] These were prepared by distillation of the oily product obtained by reaction of aldehydes with concentrated aqueous ammonia; the corresponding triazines were not isolated.[22] Our findings indicate that these undistilled crude products contain principally diimine **10**.

Diimines **10d** and **10e** were isolated as products of reaction of concentrated aqueous ammonia with pivaldehyde and 2-ethylbutanal, respectively. Examination of the nmr spectra of the crude, undistilled reaction products reveals absence of a triazine ring CH signal near δ 4; the spectra are virtually identical with those of the pure diimines. Two geometrical isomers of **10d** were isolated. In methanolic ammonia at −15° pivaldehyde produced a thermodynamically less stable isomer, mp 72–73° (70% yield). In methanol or chloroform solution at 25° it isomerized rapidly to the more stable form obtained by reaction in aqueous ammonia at 5° (mp 28–29°). This isomerization was followed in the nmr spectrum, which for the less stable form (assigned a cis,trans structure) reveals a methyl singlet at δ 0.90 that rapidly disappears,

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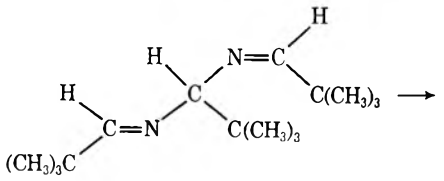
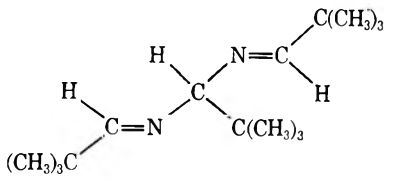
(46) H. Strecker *Justus Liebigs Ann. Chem. Suppl.*, **6**, 255 (1868).



cis,trans-**10d**



trans,trans-**10d**

leading to the methyl signal (δ 0.88) of the more stable form (assigned a trans,trans structure), Table IV.

An erroneous notion persists that unsubstituted alkylidene imines (**11**, R = alkyl) may be *synthesized*

$$\underset{\mathbf{1}}{\mathrm{RCH(OH)NH_2}} \rightleftharpoons \underset{\mathbf{11}}{\mathrm{RCH{=}NH}} + \mathrm{H_2O}$$

by pyrolysis of "aldehyde ammonias."[5,17,18,23,47,48] Although such imines would be expected to form by dehydration of 1-amino-1-alkanols (**1**), pure alkylidene imines of this type have never been isolated. Self-reaction of pure **11** occurs too rapidly to permit isolation, and pyrolysis of 2,4,6-trialkyl-1,3,5-hexahydrotriazines (**2**) takes a different reaction course. At 100–350° 2,4,6-trimethyl,1,3,5-hexahydrotriazine (**2a**) initially yields diimine **10a**, which dissociates to *N*-vinylethylideneimine (**12a**, R = CH_3; R′ = R″ = H).[44,48] Diimines having α-branched R groups behave similarly at 250°, producing high yields of *N*-vinylimines (**12**) and nitriles.[22] Aldimines produced

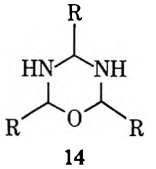
$$2 \xrightarrow[-\mathrm{NH_3}]{250^\circ} 10 \xrightarrow{250^\circ} \underset{\mathbf{12}}{\mathrm{R'R''C{=}CHN{=}CHR}} + \mathrm{RCN}$$

by pyrolysis of 2,4,6-trialkyl-1,3,5-hexahydrotriazines must be present at very low equilibrium concentrations.[44] Attempts to isolate them lead to regenerated triazines (**2**),[44] diimines (**10**),[22,44] vinylimines (**12**),[22,48] or polymers. In this respect aldimine trimers (**2**) differ from aldehyde trimers (2,4,6-trialkyl-1,3,5-hexahydrotrioxanes), which geneate isolable aldehydes on pyrolysis. Formation of alkylidene imines by photolysis of alkyl azides has been reported.[49] However, these imines were not characterized by molecular formula or spectra; their presence was inferred by isolation of the corresponding aldehyde 2,4-dinitrophenylhydrazone derivatives.[49] N-Substituted imines are more stable than those bearing an NH group.[23,48–54]

A mechanism of 2,4,6-trialkyl-1,3,5-hexahydrotriazine formation from 1-amino-1-alkanol (**1**) reasonably involves alkylidene imine **11**, acyclic dimer **13**, and trimer **9**. Other possible intermediates could include covalent hydrates of **9** and **13** [*e.g.*, RCH(OH)NHCH(NH₂)R].

$$\mathbf{1} \longrightarrow \underset{\mathbf{11}}{\mathrm{RCH{=}NH}} \xrightarrow{\mathbf{11}} \underset{\mathbf{13}}{\mathrm{RCH{=}NCH(NH_2)R}} \xrightarrow{\mathbf{11}} \mathbf{9} \rightleftharpoons \mathbf{2}$$

Stable products in addition to diimines **10** and triazines **2** are suspected in the reaction of aldehydes with ammonia. Formation of pure higher molecular weight triazines **2g** and **2h** occurs slowly in aqueous ammonia. Products isolated at intermediate reaction times are relatively lower melting and have lower nitrogen content. In addition to the NCHN proton nmr peak near δ 4.0, their spectra usually reveal an extraneous peak (broad triplet near δ 4.5, $CDCl_3$ or pyridine-d_5 solvent) assigned to an NCHO proton.[55] Diimine is not the impurity in these samples, since a vinyl methine signal near δ 7.5 is absent. A relatively low value of the total number of exchangeable protons (as determined by addition of D_2O) excludes large amounts of amino alcohol impurities. It is suggested that the contaminants in these samples are 2,4,6-trialkyl-1,3,5-hexahydrooxadiazines (**14**, R =



14

alkyl). Synthetic routes to pure **14** are under investigation.

Experimental Section[56]

Aldehydes.—All aldehydes employed were commercial samples, reagent grade, distilled immediately before use.

Preparation of Aldehyde Ammonia Hydrates (1a–i).—The general procedure may be illustrated with the preparation of **1b**. Propanal (5.8 g, 0.1 mol) was added dropwise with stirring during 10 min to concentrated (15 *M*) aqueous ammonium hydroxide (27 ml, 0.4 mol), keeping the temperature of the solution at −25° by external cooling (Dry Ice–ethylene dichloride bath). A white precipitate appeared instantly on addition of the aldehyde to the cold ammonia solution. Stirring was continued for 5 min with the temperature of the reaction mixture maintained at −25°. The product was filtered immediately with suction through a cold (−18°) jacketed sintered glass Buchner funnel, protected with a calcium chloride tube, to yield 5.0 g (39%) of **1b**, mp 15–18°. A 1.0-g aliquot of the product (removed and weighed very rapidly) was treated immediately with 25.0 ml of 1 *N* hydrochloric acid; titration with 1 *N* sodium hydroxide neutralized the excess acid (methyl red indicator); see Table I for nitrogen analysis. The product decomposed rapidly with evolution of ammonia on standing in the funnel at −18° (no suction) and within 45 min became mushy and partly liquefied.

Aldehyde ammonia hydrates **1a**, **1e**, **1g**, and **1h** were prepared (0.1-mol scale) by the procedure described above for **1b** (reaction temperature −25°) except that preparation of **1a** employed 0.44 mol of aldehyde and a 30-min addition time. Other aldehyde ammonia hydrates were prepared on a 0.1-mol scale under the conditions used for **1b** except for different reaction temperatures as follows: **1c**, −10°; **1d**, −15°; **1f**, 6°; **1i**, 3°. Properties of the aldehyde ammonia hydrates are summarized in Table I. To obtain products having the properties described requires careful

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adherence to the reaction conditions and procedures specified. Higher molecular weight alkanals such as hexanal produce instant precipitates at 0–5° or at lower temperatures. Acetaldehyde and propanal yield precipitates only at −25°; at higher temperatures they produce only clear solutions. The product (**1a**) derived from acetaldehyde is very unstable (half-life *ca.* 10 min at −18°) and very soluble in aqueous ammonia; it could be isolated only in low yield. Products derived from butanal and higher alkanals (**1c–i**) may be isolated in good yield and are relatively much more stable (half-lives of *ca.* 0.5–1 hr at 0°). Some products were washed with aqueous ammonia and/or ether prior to assay without affecting the analytical results significantly. Since products are quite unstable all samples were stored in the cold funnel (−18°, without suction) and analyzed very rapidly.

Chemical Behavior and Spectra of Aldehyde Ammonia Hydrates (1a–i).—A sample of **1a** when warmed rapidly from −18 to 25° melted and then solidified almost instantly to produce 2,4,6-trimethyl-1,3,5-hexahydrotriazine trihydrate (**2a**), mp 84–87° (identified by infrared and nmr spectra and mixture melting point determination with authentic sample). A sample of **1e**, derived from isovaleraldehyde, increased its melting point on standing at −18°. After 1 hr the melting point was 30–35° and its infrared spectrum, which now revealed no carbonyl absorption, was like that of the triazine **2f** (probably a different hydrate from one prepared by a different procedure which contains 24 water molecules; see below).

Nmr spectra of **1a–i** determined in pyridine-d_5 solvent were virtually identical with those of pure 2,4,6-trialkyl-1,3,5-hexahydrotriazines **2a–h** (Table III) in aqueous pyridine-d_5 and revealed a very strong water peak near δ 4.5–5. No aldehyde or vinyl CH signals were observed. The integrals of the water signals (relative to the ring CH and alkyl signal integrals) and the nitrogen analyses of **1a–i** indicate a molecular formula corresponding to a 1:1 adduct of aldehyde and ammonia with two to four molecules of water of hydration. The water assays and nitrogen analyses varied slightly in parallel runs and with the age of the sample. Water assays could also be roughly determined by diluting weighed samples with isopentane and measuring the volume of the lower water layer, or by adding anhydrous magnesium sulfate to the isopentane solution and determining the gain in weight of the hydrated sulfate after filtration and washing with isopentane (see procedure under preparation of **2c**, below). The infrared spectra of **1a–i** were determined at 25° on fresh samples (rapidly prepared Nujol mull or KBr disk) and scanning the spectrum as rapidly as possible. Spectra were all similar in showing very strong NH and OH bands near 3400 cm^{-1} and carbonyl and C=N bands near 1720 and 1650 cm^{-1}, respectively. The product of highest melting point (**1d**), derived from pentanal, produced an infrared spectrum (mull) showing very strong OH and NH bands and relatively weak C=O and C=N bands. On standing at 25°, the C=O and C=N band intensities rapidly increased.

2,4,6-Trialkyl-1,3,5-hexahydrotriazines (2a–h).—These were prepared by addition of aldehydes to 4 molar equiv of 15 *M* concentrated aqueous ammonia at 0–5° followed by storage at 0°. Nitrogen analyses by titration, and water assays of hydrates of **2a–h**, were determined by the methods described above for **1a–i**; data are summarized in Table II. Proton nmr spectra of triazines **2a–h** are summarized in Table III.

2,4,6-Trimethyl-1,3,5-hexahydrotriazine trihydrate (2a trihydrate) was prepared by the procedure of Aschan,[9] 75% yield, mp 94–95°. A sample of "acetaldehyde ammonia," mp 92–95°, supplied by Aldrich Chemical Co., had properties identical with those of **2a** trihydrate. The anhydrous form (**2a**) was prepared by drying at ambient temperature in a vacuum desiccator over calcium chloride, mp 94–96°.

2,4,6-Triethyl-1,3,5-hexahydrotriazine (2b).—Propanal (58.2 g, 1.0 mol) was added to concentrated (15 *M*) aqueous ammonium hydroxide (266 ml, 4.0 mol) during 10 min, keeping the temperature below 5° (ice-bath cooling). No precipitate was observed during this time. The clear, homogeneous solution was stored at 0° for 5 days. Sodium chloride (80 g) was added and the mixture was stirred at room temperature for 1 hr, then extracted with four 100-ml portions of ether. The combined ether extracts were dried with magnesium sulfate, filtered, and concentrated under reduced pressure and then pumped at 0.1 mm for 1 hr to yield 57.0 g of crude **2b**, mp 0–3° (temperature maintained below 25° during work-up). The crude product was dissolved in ether and stirred with Drierite for 5 min, filtered, and concentrated to yield 50.6 g (89%) of **2b**, mp 2–3° (analytical sample). The product could be distilled, bp 55–60° (10 mm), but with decomposition to yield a mixture of **2b** and diimine **10b** (*ca.* $^2/_3$ **2b** by nmr assay).

Addition of 3 molar equiv of water to a sample of anhydrous **2b** produced its trihydrate on chilling, mp 13–15°. Addition of 1 molar equiv of water gave a solution which did not crystallize at −15°, and addition of 18 molar equiv of water gave crystals, mp 4–5°. These hydrates are soluble in 15 *M* aqueous ammonium hydroxide at 0°.

2,4,6-Tripropyl-1,3,5-hexahydrotriazine (2c).—Butanal (36.0 g, 0.5 mol) was added to concentrated (15 *M*) aqueous ammonium hydroxide (133 ml, 2.0 mol) with stirring during 15 min (5–10°). A white precipitate of aldehyde ammonia **1c** formed immediately on addition of the aldehyde. After *ca.* 90 min storage at 0° this initial precipitate had changed to a floating oily layer. Storage at 0° for 8 days gave a large amount of crystals mixed with some oil. The mixture was filtered through a jacketed (−6°) sintered glass Buchner funnel and washed successively with cold 15 *M* ammonia, ice water, and cold isopentane to yield 59.9 g (67%) of **2b** octadecahydrate, mp 28–30°. Shorter reaction times gave lower yields: 4 days, 58%; 1 day, 36%. On melting, the hydrate produced two liquid layers which resolidified on chilling, mp 28–30°. A 2.0-g sample of the hydrate in 25 ml of methylene chloride was stirred with magnesium sulfate (3.00 g) for 1 hr to yield 4.22 g of magnesium sulfate hydrate after filtration and washing with methylene chloride; the gain in weight of the sulfate corresponds to 18.5 molar equiv of water of hydration. The nmr spectrum of the hydrate (pyridine-d_5) showed δ 5.10 (s, 40, 18.5 H_2O and 3 NH), 3.88 (t, $J \cong 6$ Hz, 3, CH), 1.2–2.0 (m, 12, CH_2CH_2), 0.96 (t, $J = 6$ Hz, 9, CH_3).

A 7.5-g sample of the hydrate at 0° was pumped at 0.05 mm for 18 hr to yield 2.6 g (90%) of crude anhydrous triazine **2c**; purification was achieved by dissolving in isopentane and drying with Drierite for 10 min; filtration, followed by concentration at 25° and pumping at 0.1 mm for 10 min, gave pure **2c**, mp 6–8°. Addition of excess water to anhydrous **2c** regenerated the hydrate, mp 24–28°.

2,4,6-Triisopropyl-1,3,5-hexahydrotriazine (2d).—The procedure employed in preparation of **2c** was used (0.5 mol of isobutyraldehyde). A floating oily layer formed during the addition, but no solid was observed. After storage at 0° for 24 hr, crystals which had formed were removed by filtration through the cold funnel and washed with ice water to yield 31.0 g of slightly wet **2d** as white crystals, mp 21–22°; the nmr spectrum (pyridine-d_5) revealed no water peak near δ 5; addition of D_2O to the sample produced a water peak at δ 5.62 corresponding to *ca.* four protons (3 NH and *ca.* 0.5 H_2O); reaction of a 2.00-g sample with 3.00 g of anhydrous magnesium sulfate (as with **2c**) produced a weight gain of only 0.02 g. A 3.0-g aliquot dissolved in 30 ml of isopentane to produce a slightly turbid solution, but no water layer; the solution was dried as with **2c** to yield 2.7 g (78%) of pure **2d**, mp 26–27°.

2,4,6-Triisobutyl-1,3,5-hexahydrotriazine (2f).—The procedure employed for preparation of **2c** was used (0.5 mole of isovaleraldehyde; 10 min addition time). A precipitate of isovaleraldehyde ammonia hydrate (**1e**) formed immediately on addition of the aldehyde to the ammonia; on storage at 0° no liquefaction of the initial precipitate was observed (as in the preparations of **2c** and **2e**); a white precipitate was present during the entire period of storage at 0° (1 month). The crystals were removed by filtration and washed with ice water to yield 63.5 g (92%) of **2f** hydrate (24 H_2O), mp 58–60°. The nmr spectrum of the hydrate (pyridine-d_5) showed δ 5.18 (s, 51, 24 H_2O and 3 NH), 4.00, (t, $J \cong 6$ Hz, 3, ring CH), 1.7–2.3 (m, 3, isopropyl CH), 1.4–1.8 (m, 6, CH_2), 0.92 (d, $J = 6$ Hz, 18, CH_3). A 20.0-g sample of the hydrate was melted by gentle heating in a water bath to yield two layers, and the water layer (*ca.* 12 ml) was removed with a pipette. The remaining liquid was dissolved in 50 ml of isopentane, dried with Drierite, and purified as described for **2c** to yield 7.5 g of crude triazine **2f**, mp 21–23°. Some decomposition occurred during the dehydration process leading to a product having some C=N, but no C=O, absorption in the infrared spectrum (1650 cm^{-1}); the nmr spectrum revealed triplet signals at δ 4.9 and 7.8, characteristic of a diimine (**10**, R = i-C_4H_9), which are absent in the hydrate. Other methods of dehydration, including pumping at 0° (0.05 mm) and drying in isopentane at 25°, also produced samples of triazine **2f** containing some diimine **10** (*ca.* 20% by nmr assay and titration; see Table II). Addition of water to **2f** regenerated the hydrate (24 H_2O), purified by filtration and washing with isopentane.

2,4,6-Trialkyl-1,3,5-hexahydrotriazines 2e, 2g, 2h and their hydrates were prepared by the procedure employed for **2c** except for reaction times of 18 days for **2e** and 3 months for **2g** and **2h**.

***N,N'*-Bis(2-ethylbutylidene)-2-ethyl-1,1'-diaminobutane (10e).**—2-Ethylbutanal (50.1 g, 0.5 mol) was added, with stirring, to concentrated (15 *M*) aqueous ammonium hydroxide (133 ml, 2.0 mol) during 3 min (reaction temperature 5–6°) to produce an oil. The mixture was stored at 0°; small aliquots were removed from the floating oily layer at intervals to determine infrared and nmr spectra. During 2 weeks the aldehyde carbonyl band at 1720 cm^{-1} slowly disappeared while the C=N band at 1650 cm^{-1} increased in intensity. After 2 weeks the oily product revealed an nmr spectrum virtually identical with that of pure **10e**; no proton signal was observed near δ 4 characteristic of 2,4,6-trialkyl-1,3,5-hexahydrotriazines. After 3 months' storage at 0° the oil was separated (virtually no change in nmr or ir spectra from that observed at 2 weeks); the aqueous layer was extracted with hexane; and the oil and combined hexane extracts were dried with Drierite. Distillation produced 3.8 g, bp 40–60° (5–13 mm), containing some 2-ethylbutanal (C=O band at 1725 cm^{-1}), and 37.9 g (81%) of **10e**: bp 107–110° (3 mm); $n^{25}D$ 1.4543; ν (neat) 1670 cm^{-1} (C=N), carbonyl bands absent; nmr data in Table IV.

Anal. Calcd for $C_{18}H_{36}N_2$: C, 77.07; H, 12.94; N, 9.99; mol wt, 280.5. Found: C, 77.18; H, 13.04; N, 9.86 (Dumas), 9.78 (titration); mol wt, 278 (osmometry, chloroform).

***cis,trans-N,N'*-Bis(2,2-dimethylpropylidene)-2,2-dimethyl-1,1-propanediamine (*cis,trans*-10d).**—Pivaldehyde (8.6 g, 0.10 mol) was dissolved in 9.7 *M* methanolic ammonia (40 ml, 0.40 mol) and stored at −15°; within 20 min a precipitate began to form. After 5 days at −15° the product was filtered through a cold-jacketed funnel and washed with cold (−15°) methanol to yield 5.6 g (70%) of *cis,trans*-**10d** as large, colorless rectangular prisms, mp 72–73°, ν (KBr) 1650 cm^{-1} (C=N), nmr data in Table IV.

Anal. Calcd for $C_{15}H_{30}N_2$: C, 75.56; H, 12.68; N, 11.75; mol wt, 238.4. Found: C, 75.65; H, 12.72; N, 11.68; mol wt, 243 (osmometry, chloroform).

Isovaleraldehyde, hexanal, heptanal, and 2-ethylbutanal were treated with *ca.* 10 *M* methanolic ammonia in procedures similar to that used with pivaldehyde (3–30 days' reaction time). Products isolated were oils at ambient temperature and contained principally the same compounds produced with 15 *M* aqueous ammonia as a reactant.

***trans,trans-N,N'*-Bis(2,2-dimethylpropylidene)-2,2-dimethyl-1,1-propanediamine (*trans,trans*-10d).**—Pivaldehyde (43.1 g, 0.5 mol) was added dropwise with stirring to 15 *M* aqueous ammonia (133 ml, 2.0 mol) during 5 min (6–8°). Within *ca.* 10 min at 0° a voluminous white precipitate (mp 45–48°) was produced. After standing with the aqueous ammonia at 25° for 4 hr the precipitate had changed to an oil. Continued storage at 0° for 6 days produced white crystals, 32 g of crude product, mp 20–22°; it was dissolved in isopentane and dried with Drierite to yield 24.6 g, mp 24–28°, found 13.1% N by titration. Distillation gave 22 g (55%) of *trans,trans*-**10d**: bp 78° (9 mm); mp 28–29°; ir (neat liquid) 1650 cm^{-1} (C=N); the ir spectrum was practically identical with that observed for *cis,trans*-**10d**.

Anal. Calcd for $C_{15}H_{30}N_2$: C, 75.56; N, 12.68; N, 11.75; mol wt, 238.4. Found: C, 74.63; H, 12.55; N, 11.63 (Dumas), 11.77 (titration); mol wt, 250 (osmometry, chloroform).

***N,N'*-Dipropylidene-1,1-diaminopropane (10b).**—2,4,6-Triethyl-1,3,5-hexahydrotriazine (**2b**) (10 g, 0.0584 mol) dissolved in 1 l. of hexane was heated under reflux for 7 hr. The solution was concentrated and the residue was distilled to yield 7.2 g (80%) of colorless **10b**: bp 48–50° (5 mm); $n^{25}D$ 1.4465; d^{25}_4 0.857; ir (neat) 1650 cm^{-1} (C=N); nmr, Table IV; 1.5 g of yellow residue remained. The distillate polymerized and became viscous on standing. A freshly distilled sample was employed immediately for analysis.

Anal. Calcd for $C_9H_{18}N_2$: N, 18.16. Found: N, 18.3 (titration).

The procedure used for preparation of **10b** was repeated with 2,4,6-trimethyl-1,3,5-hexahydrotriazine (**2a**) (18-hr reflux) to yield, after removal of the hexane by distillation, an oil containing *ca.* 10% of recovered **2a** and 90% of *N,N'*-bisethylidene-1,1'-diaminoethane (**10a**) (nmr assay; Table IV). The product polymerized rapidly on standing and/or heating.[44] The procedure was also repeated with 2,4,6-triisobutyl-1,3,5-hexahydrotriazine (**2f**) (reflux time 4 hr) to yield a fraction, bp 100–111° (3 mm), containing unidentified impurities and *N,N'*-diisobutylidene-1,1-diamino-3-methylbutane, nmr ($CDCl_3$) δ 7.72 t (J = 4.5 Hz, CH=N), 4.25 t (J = 6 Hz, CH).

***N,N'*-Diisobutylidene-1,1-diamino-3-methylpropane (10c).**—2,4,6-Triisopropyl-1,3,5-hexahydrotriazine (**2d**) (10.0 g, 0.047 mol) was distilled through a short Vigreux column to yield 8.0 g (87%) of **10c**: bp 78–80° (12 mm); $n^{25}D$ 1.4375 (lit.[22] $n^{20}D$ 1.4391); d^{25}_4 0.830; ir (neat) 1650 cm^{-1} (C=N); nmr, Table IV. Vigorous evolution of ammonia occurred during the initial heating.

Anal. Calcd for $C_{12}H_{24}N_2$: C, 73.41; H, 12.32; N, 14.27; mol wt, 196.3. Found: C, 73.23; H, 12.26; N, 14.13; mol wt, 200 (osmometry, chloroform).

A mixture of 3.92 g (0.02 mol) of **10c** and 16 ml of 15 *M* aqueous ammonia was stored at 0° for 1 week to yield 4.0 g (94%) of 2,4,6-triisopropyl-1,3,5-hexahydrotriazine (**2d**), mp 20–22° (identified by ir and nmr spectra and mixture melting point with an authentic sample).

***N,N'*-Dibenzoyl-1,1-diaminoethane (6).**—2,4,6-Trimethyl-1,3,5-hexahydrotriazine trihydrate (1.84 g, 0.01 mol) was added to 5 ml of ethanol and 14 ml of 10% aqueous sodium hydroxide solution. Benzoyl chloride (4.6 g, 0.033 mol) was added dropwise with shaking to yield 0.52 g (20%) of **6**, mp 200–202°. Recrystallization from ethanol gave long needles: mp 202–204° (lit. mp 204°,[57] 202–204°[40]); nmr (DMSO-d_6) δ 8.72 s, 8.60 s (2, NH), 7.9–8.2 m (4, *m*-C_6H_5), 7.2–7.7 m (6, *o,p*-C_6H_5), 6.35 q, 6.23 q (1, CH), 1.67 (d, 3, CH_3). The nmr spectrum in DMSO-d_6 suggests the presence of two conformers (1:1 ratio) which exist owing to restricted rotation about the amide C–N bonds.

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44; mol wt, 268.3. Found: C, 71.42; H, 6.05; N, 10.28; mol wt, 279 (osmometry, chloroform).

***N,N'*-Bis(phenylcarbamoyl)-1,1-diaminoethane (7).**—To anhydrous 2,4,6-trimethyl-1,3,5-hexahydrotriazine (**2a**) (1.29 g, 0.01 mol) in 10 ml of tetrahydrofuran was added phenyl isocyanate (3.6 g, 0.01 mol) and the mixture was allowed to stand at ambient temperature for 24 hr. Removal of solvent, followed by crystallization from benzene, gave 0.25 g (8%) of **7**, mp 215–217°. Recrystallization from ethanol gave needles: mp 225° (lit.[42] mp 220°); nmr (DMSO-d_6) δ 8.50 s (2, NH), 6.4–7.6 m (12, C_6H_5 and NH), 5.33 q (1, CH), 1.42 d (3, CH_3).

Anal. Calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78; mol wt, 298.34. Found: C, 64.06; H, 6.19; N, 18.06; mol wt, 301 (osmometry, DMF).

Registry No.—**1a**, 75-39-8; **1b**, 40898-94-0; **1c**, 40898-95-1; **1d**, 40898-96-2; **1e**, 40898-97-3; **1f**, 40898-98-4; **1g**, 40898-99-5; **1h**, 40899-00-1; **1i**, 40899-01-2; **2a**, 638-14-2; **2b**, 102-26-1; **2c**, 40899-04-5; **2d**, 40899-05-6; **2e**, 40899-06-7; **2f**, 40899-07-8; **2g**, 40899-08-9; **2h**, 40899-09-0; **6**, 40899-10-3; **7**, 40899-11-4; **10a**, 623-75-6; **10b**, 40899-13-6; **10c**, 28916-22-5; *cis,trans*-**10d**, 40899-15-8; *trans,trans*-**10d**, 40899-16-9; **10e**, 40899-17-0; propanal, 123-38-6; acetaldehyde, 75-07-0; isovaleraldehyde, 590-86-3; butanal, 123-72-8; isobutyraldehyde, 78-84-2; 2-ethylbutanal, 97-96-1; pivaldehyde, 630-19-3; benzoyl chloride, 98-88-4; phenyl isocyanate, 103-71-9.

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Homogeneous Catalyzed Reduction of Nitro Compounds. I. The Synthesis of Oximes

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Received April 24, 1973

Copper salts solubilized in alkylpolyamine solvents have been found to promote the homogeneous reduction of nitroalkanes to oximes by carbon monoxide in good yields and conversions. Catalysis is favored by the use of cuprous salts of weak acids solubilized in alkylpolyamine solvents of $pK_a > 9.2$. The suggested reaction path involves the formation of a copper–nitroalkane complex by combination of the solvated cuprous carbonyl with the nitroalkane anion and is followed by CO insertion into the copper–oxygen bond of the said complex. Silver salts also catalyze the synthesis of oximes under more stringent conditions.

The action of CO upon solutions of copper salts leads to the formation of cuprous CO complexes that have pronounced activity as reducing agents.[1] Brackman has demonstrated that the activity of cuprous CO complexes toward certain oxidizing agents is considerably enhanced through coordination of the metal with appropriate ligands, and that coordination with amines, in particular, will greatly increase the activity of the CO adduct.[2] Copper salts in piperidine and other secondary amines when treated with CO, for example, will reduce such diverse oxidants as copper(II) amines, nitrobenzene, and methylene blue.[2] The nitrobenzene reduction products were not identified in that work, but a similar cuprous CO adduct is probably the active intermediate in the reported[3] reduction of nitrobenzene to aniline by CO and solutions of copper acetate in aqueous amine.

As part of a program to examine the utility of homogeneous catalysis for effecting reactions of $C–NO_2$ compounds, we report here that solutions of cuprous salts in amine solvents are excellent catalysts for the selective CO reduction of nitroalkanes to the corresponding oximes.[4] This represents one of the first examples of the use of homogeneous catalysis for reducing nitroalkanes.[5] Kinetic studies, together with a general examination of the scope of the reaction, have been carried out in order to gain some understanding of the mechanism of this catalysis.

Results and Discussion

Synthesis.—The selective reduction of nonaromatic nitro compounds to oximes by CO and solutions of copper salts is a fairly general synthesis technique that is applicable to both linear and cyclic, primary and secondary nitroalkanes and nitroalkanes in dilute paraffin streams such as may be obtained by paraffin nitration. The method requires mild experimental conditions and allows ease of product separation. While preferred conditions can, to some extent, be determined by the nature of the nitro compound, generally catalysis is favored by the use of copper(I) salts of weak acids, such as cuprous acetate, solubilized in highly basic alkylpolyamine solvents like 1,3-propanediamine and 1,6-hexanediamine. In contrast to most other methods for preparing aliphatic oximes from nitroalkanes,[6] this synthesis is truly catalytic, and reasonable reaction rates have been achieved at substrate–copper mole ratios of 100.

Summarized in Table I are typical syntheses data for the preparation of $C_3–C_{12}$ aliphatic oximes. The oximes were obtained in 52–89% yields; the aldoxime, propanal oxime, was found to undergo rapid secondary reactions, and no effort was made to optimize the yield of this product. Among other nitroalkanes, the general order of reactivity is 1-nitroalkanes > 2-nitroalkanes > 3–6-nitroalkanes, but with mixtures of nitroalkanes, the copper(I) solutions are not sufficiently selective to sequentially reduce the individual homologs.

Kinetic Studies.—The reaction of carbon monoxide with solubilized copper salts has been investigated by several groups of workers.[1,2,7] In aqueous media, reduction of copper(II) to copper(I) may proceed by more than one path,[1] and may lead, *via* the formation of CO insertion complexes, to the stable cuprous carbonyl complex, $Cu(CO)^+$.

$$2Cu(II) + 3CO + H_2O \longrightarrow 2Cu(CO)^+ + CO_2 + 2H^+ \quad (1)$$

In the absence of additional substrate, the solvated cuprous carbonyl will undergo reduction to the metal, disproportionation, or hydrolysis, depending upon the prevailing chemical conditions. In the presence of nitroalkanes, we find the major products to be oximes, with concomitant oxidation of the CO to CO_2. The reduction of nitrocyclohexane to cyclohexanone oxime by cuprous acetate–ethylenediamine solutions has been studied in some detail in this work, and the *initial* rate was found to be first order in copper, at least over the concentration range 5–50 m*M* Cu (see Figure 1). Deviations from first-order kinetics are evident at higher copper concentrations, where reduction may become diffusion controlled or, more likely, dimerization of the copper complex becomes important. Wright, for example, has reported significant polymerization of cuprous acetate in amine solutions at concentrations above 0.1 *M*.[8] A typical rate plot, also showing the formation of cyclohexanone oxime, is reproduced in Figure 2.

That cuprous ion is important in the catalyst cycle is demonstrated by the following observations: (a) catalyst solutions containing nitroalkane and CO

(1) J. J. Byerley and E. Peters, *Can. J. Chem.*, **47**, 314 (1969).
(2) W. Brackman, *Discuss. Faraday Soc.*, **46**, 122 (1968).
(3) H. R. Appell, *J. Org. Chem.*, **32**, 2021 (1967).
(4) J. F. Knifton, British Patent 1,269,483 (1972).
(5) For the reduction of nitro compounds *via* homogeneous catalysis see also (a) F. L'Eplatterier, P. Matthys, and F. Calderazzo, *Inorg. Chem.*, **9**, 342 (1970); (b) J. E. Kmiecik, *J. Org. Chem.*, **30**, 2014 (1965); (c) J. Kwiatek, *Catalysis Rev.*, **1**, 37 (1967); (d) S. Murahashi and S. Horiie, *Bull. Chem. Soc. Jap.*, **33**, 78 (1960).
(6) See P. A. S. Smith, "Open Chain Nitrogen Compounds," Vol. II, W. A. Benjamin, New York, N. Y., 1966, Chapters 8 and 14.
(7) J. J. Byerley and J. Y. H. Lee, *Can. J. Chem.*, **45**, 3025 (1967).
(8) L. W. Wright, S. Weller, and G. A. Mills, *J. Phys. Chem.*, **59**, 1060 (1955).

TABLE I
SYNTHESES OF ALIPHATIC OXIMES FROM NITROALKANES CATALYZED BY CUPROUS SALTS IN ALKYLPOLYAMINES[a]

Nitroalkane	Solvent	Conversion, mol %	Major product[b]	Yield, mol %[c]
1-Nitropropane	1,6-Hexanediamine	100	Propanal oxime	52[d]
2-Nitropropane	1,6-Hexanediamine	>95	Acetone oxime	58[d]
1-Nitroheptane	1,3-Propanediamine	100	Heptanal oxime	76
Nitrocyclohexane	1,3-Propanediamine	100	Cyclohexanone oxime	89
Nitrododecanes[e]	1,3-Propanediamine	100	Dodecanone oximes	85
Nitrated *n*-dodecane[f]	1,3-Propanediamine	100	Dodecanone oximes	84

[a] Experimental conditions: 2.5–5.0 mmol Cu; 25–50 mmol RNO_2; 85°, 1 atm CO. [b] Oximes were identified by comparison of melting points or boiling points (see Experimental Section) and spectral properties (infrared, nmr) with those reported in the literature. [c] Based upon moles of nitroalkane charged. [d] Estimated by gas chromatography by comparison with authentic samples. [e] An isomeric mixture of 2- through 6-nitrododecanes. [f] A mixture of 25.9% (v/v) nitrododecanes, 64.1% (v/v) *n*-dodecane, and 10% other materials including dodecanones, prepared by liquid–vapor phase nitration of *n*-dodecane.

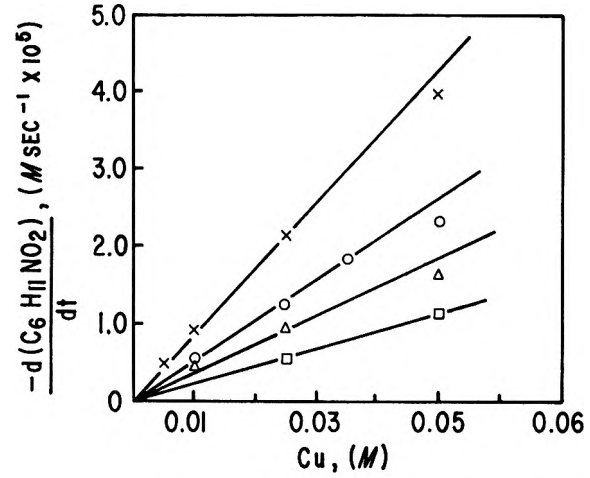


Figure 1.

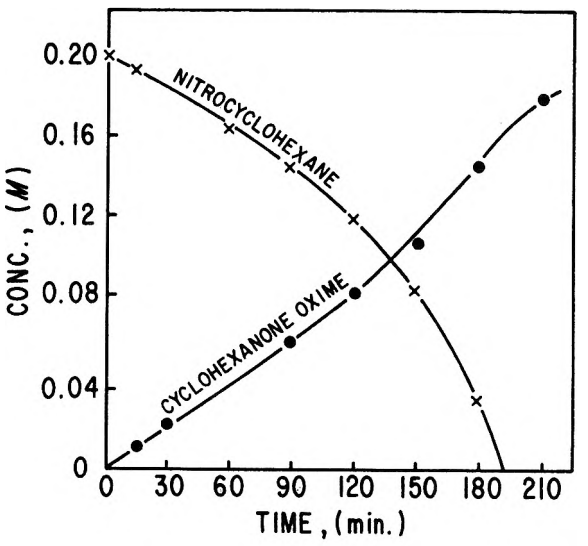


Figure 2.

remain pale yellow [indicative of copper(I) in amines[9]] throughout the reduction to oxime; (b) initially blue-colored solutions of the corresponding copper(II) salts reduce the nitroalkane at a markedly slower rate; and (c) solutions of cuprous acetate, and those of cupric acetate that have been pretreated with CO until pale yellow, show very similar rates of reduction (Table II). No nitroalkane reduction was detected in the absence of metal complex. The reaction mixture remains homogeneous throughout the formation of oxime, and there is no evidence, at least in dilute solution, for further reduction of the copper(I) to the metal or hydrolysis to the oxide. Identical results were obtained with or without the addition of glass beads.

The importance of carbon monoxide beyond that of reducing cupric ions is seen by the fact that, under almost stoichiometric conditions, no cyclohexanone oxime was detected with mixtures of nitrocyclohexane and cuprous acetate–ethylenediamine solutions in the absence of CO, *i.e.*, under a nitrogen blanket (see Table II). This points to the importance of a cuprous carbonyl moiety in the catalytic cycle, rather than nitro reduction *via* a redox mechanism[10] involving cuprous ion. As to the nature of the cuprous carbonyl complex responsible for nitroalkane reduction, it has been claimed[11] that each cuprous ion can bind only one CO molecule, and this is consistent with the $Cu(CO)^+$ ion being a critical intermediate in the copper-catalyzed reduction of other substrates by carbon monoxide.[7]

TABLE II
CYCLOHEXANONE OXIME SYNTHESIS CATALYZED BY COPPER SALTS. CATION–ANION EFFECTS[a]

Solubilized copper salt	Reducing atmosphere	Initial rate of nitrocyclohexane reduction, M sec^{-1} × 10^6
Copper(II) acetate monohydrate[b]	CO	4.64
Copper(II) acetylacetonate monohydrate[b]	CO	12.7
Copper(II) carbonate[b]	CO	4.17
Copper(II) chloride dihydrate[b]	CO	1.32
Copper(II) sulfate pentahydrate[b]	CO	<0.1
Copper(I) acetate	CO	5.26
Copper(I) cyanide	CO	<0.1
Copper(I) acetate[c]	N_2	No reaction

[a] Run conditions: 10 mM Cu; 0.25 M RNO_2; solvent, ethylenediamine; 95°; 1 atm CO. [b] All solutions of copper(II) salts were pretreated with CO until decolorized. [c] 50 mM Cu; 100 mM RNO_2.

Recently, Rucci, *et al.*,[12] reported an analogous copper(I) ethylenediamine carbonyl complex, [Cu(en)(CO)]-

(9) S. Weller and G. A. Mills, *J. Amer. Chem. Soc.*, **75**, 769 (1953).
(10) G. Battistuzzi Gavioli, G. Grandi, and R. Andreoli, *Collect. Czech. Chem. Commun.*, **36**, 730 (1971), and references cited therein.
(11) R. Stewart and D. G. Evans, *Anal. Chem.*, **35**, 1315 (1963).
(12) G. Rucci, C. Zanzottera, M. P. Lachi, and M. Carnia, *Chem. Commun.*, 652 (1971).

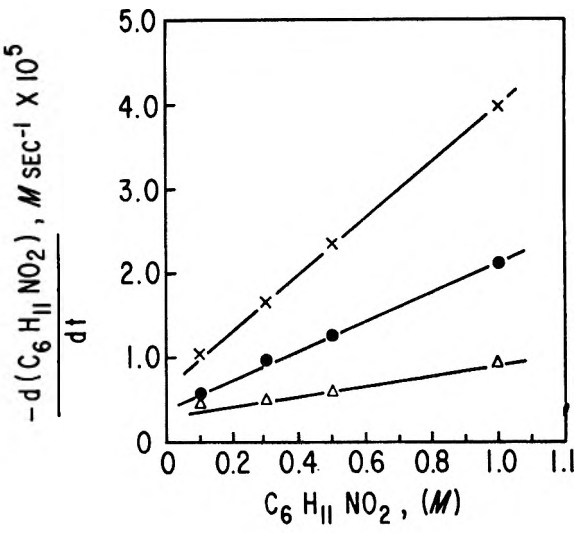


Figure 3.

Cl, and its dimer, which are sufficiently stable to be isolated from copper(I)–amine solutions. A somewhat similar copper(I) carbonyl complex would be expected to be formed in this work with CO-treated solutions of cuprous salts in ethylenediamine (eq 2).

$$L_xCu(I) + CO \longrightarrow [L_xCu(CO)]^+ \quad (2)$$

The dependence of the initial rate upon nitrocyclohexane concentration is shown in Figure 3 for three copper concentrations. The linear dependence over the RNO_2 range 0.1–1.0 M is indicative of pseudo-first-order kinetics. Generally, the selective reduction of nitroalkanes to alkyl oximes proceeds *via* the prior formation of the more reactive nitroalkane anion.[6,13] While the equilibrium constants for the ionization of short-chain primary and secondary nitroalkanes in aqueous media are of the order 10^{-8}–10^{-10} (see ref 14), in highly basic alkylamine solvents the nitroalkane molecule will be extensively deprotonated to the anionic form[6] (eq 3). Thus it is this anionic species which is

$$RR'CHNO_2 + B: \rightleftharpoons [RR'CNO_2]^- + BH^+ \quad (3)$$

likely to be involved in the reduction sequence (see below) leading to the formation of the oxime. In this work, the prior formation of the nitro anion in alkylamine solutions has been confirmed by an intense band in the near-ultraviolet at about 232 mμ.[15]

Although the linear dependence is evident in Figure 3, the plots do not pass through the origin. This suggests faster rates at low nitrocyclohexane concentrations (below *ca.* 0.1 M). The divergence may be due to a second reaction path which is effectively zero order in nitroalkane. Alternatively, dimerization of the nitroalkane anion[6] at higher concentrations could be effectively decreasing the rate values and consequently shifting the plots away from the origin but still maintaining the approximately linear relationship. An extensive study of this low nitrocyclohexane concentration region (<0.1 M) would have been desirable, but difficulties were encountered in obtaining reproducible values.

(13) J. Von Braun and O. Kniber, *Chem. Ber.*, **46**, 384 (1912).
(14) D. Turnbull and S. H. Maron, *J. Amer. Chem. Soc.*, **65**, 212 (1943).
(15) F. T. Williams, R. P. K. Flanagan, W. J. Taylor, and H. Shechter, *J. Org. Chem.*, **30**, 2674 (1965).

The important role played by the amine solvent in determining the course of the nitroalkane reduction can be readily seen from the data summarized in Table III. Here nitrododecane reduction by CO and cuprous acetate was examined in a number of structurally different solvents. Only strongly basic alkylpolyamines were found satisfactory for the synthesis of the oximes. Both in the case of nitrododecane and nitrocyclohexane, no oxime was detected with solvents of base strength less than about 9.2 pK_a units; these include typical chelating and nonchelating alkylamines as well as hetrocyclic bases. On the other hand, some reduction of the nitrododecane was detected with all solvents of pK_a greater than about 9.2 units. Good yields of dodecanone oxime were achieved with alkylpolyamines such as 1,6-hexanediamine, 1,3-propanediamine, ethylenediamine, and 3,3′-iminobispropylamine.

TABLE III

CO REDUCTION OF NITRODODECANE CATALYZED BY CUPROUS ACETATE IN VARIOUS AMINE SOLVENTS[a,b]

Solvent Composition	pK_a[c]	Major products	Rate of nitrododecane reduction, M sec^{-1} × 10^6
Pyridine	5.45	No reaction	
Morpholine	8.70	No reaction	
Diethanolamine	9.00	No reaction	
N,N,N′,N′-Tetramethylethylenediamine[d]	9.14	No reaction	
Benzylamine	9.34	Dodecanone + dodecylamine	*e*
Tetraethylenepentamine	9.9	Dodecanone oxime	2.5
Diethylenetriamine	9.94	Dodecanone oxime	5.6
Ethylenediamine	10.18	Dodecanone oxime	8.1
n-Hexylamine	10.4	Dodecanone + dodecylamine	*e*
1,3-Propanediamine	10.62	Dodecanone oxime	27.6
3,3′-Iminobispropylamine	10.65	Dodecanone oxime	26.4
1,6-Hexanediamine	11.1	Dodecanone oxime	24.0
Piperidine	11.28	Dodecanone + dodecylamine	*e*

[a] A mixture of isomers 2- through 6-nitrododecanes. [b] Run conditions: 0.1 M Cu, 0.5 M RNO_2, 85°, 1 atm CO. [c] Data taken from "Stability Constants of Metal-Ion Complexes," Section II: Organic Ligands, Chemical Society Special Publication No. 17, 1964, and Supplement No. 1, Special Publication No. 25, 1971; H. K. Hall, *J. Amer. Chem. Soc.*, **79**, 5441 (1957). [d] Some catalyst precipitation with this solvent. [e] Not determined.

Other strongly basic monoamines like *n*-hexylamine and piperidine gave a mixture of products, including some dodecanone oxime, dodecylamine (by further reduction that may involve an internal redox reaction of the copper–alkylamine complex[16]), and carbonyl derivatives[2] including ketones *via* a Nef-type reaction.

While the conditions under which these amine pK_a's were measured (25°, 0.5–1.0 μ) are far removed from the experimental conditions employed here for nitroalkane reduction, nevertheless it is reasonable to assume

(16) W. Gerrard, M. Goldstein, and L. F. Mooney, *J. Inorg. Nucl. Chem.*, **31**, 107 (1969).

that the pK_a data give a fair indication of the *relative* base strengths of the different solvents under the conditions specified in Table III. The function of the amine solvent in the nitroalkane reduction sequence may be at least threefold. Firstly, the more basic solvents will favor the formation of the nitroalkane anion by shifting the equilibrium 3 further to the right. Secondly, the amine solvents will stabilize the cuprous ions against disproportionation to the metal and copper(II).[17] Certainly in this work it was noticeable that solutions of copper(II) acetate in solvents like piperidine were much more rapidly decolorized by CO treatment than with solvents such as pyridine. Thirdly, the more basic amines, as better σ donors to the copper, may promote the electron-transfer steps involved in the reduction to oxime.

The effect of base upon the activity of cuprous salts has been noted previously. Weller and Mills report that the catalytic activity of cuprous salts in organic bases varies significantly with the base strength of the solvent.[9] In a related case, Nakamura and Halpern found that, while the reduction of Ag^+ by CO in aqueous perchloric acid solution is slow even at elevated temperatures (>100°), the addition of ammonia or amine enhances the reactivity of the silver to the degree that reduction proceeds at room temperature.[18] This marked enhancement in reactivity toward CO was attributed to the increase in pH rather than effects associated specifically with complexing of the Ag^+ ion.

Further evidence for the importance of solvent composition in the oxime synthesis can be seen from the data summarized in Table IV. Here the relative rates

TABLE IV

DODECANONE OXIME SYNTHESIS CATALYZED BY COPPER ACETATE IN AQUEOUS ETHYLENEDIAMINE[a]

Solvent composition: concentration (v/v) of aqueous component	Relative rate of nitrododecane reduction
<2	1.0
5	0.9
10	0.55
30	0.04
50	<0.01

[a] Run conditions: 0.5 *M* Cu, 0.5 *M* RNO_2, 85°, 1 atm CO.

of reduction of nitrododecane were measured in mixed aqueous–ethylenediamine solutions. As with the CO reduction of nitrobenzene,[3] a marked dropoff in rate was observed with solutions containing more than 10% water.

Among the alkylpolyamine solvents described in Table III, the relative rates of nitrododecane reduction are also in line with the solvent base strengths. The effectiveness of the polyamines as chelating agents is apparently unimportant and may actually retard the rate. For example, diethylenetriamine and tetraethylenepentamine, which both have the capacity to form multiring complexes are considerably less effective than the more basic 1,6-hexanediamine, which is not a chelating agent. The results can be rationalized on the basis of copper(I) chemistry, where chelation in copper(I) multidentate amine complexes is generally either unimportant or leads to ring strain. Witness the cumulative equilibrium constants (log β_2) for cuprous ammine and ethylenediamine complexes, which are both reported[19] as about 10.8. This does not preclude the possibility, however, of bridged ligand complexes, where the polyamine is bonded to two or more copper atoms.

Anion effects also play a role in determining the activity of the copper catalyst. Generally, reduction is favored by the presence of copper salts of weak acids, such as copper acetate (see Table II); sulfate and chloride salts are less active; and cyanide deactivates the catalyst, probably by displacing the carbon monoxide.[2]

It is unlikely, under the conditions of these experiments, that these anions will displace the alkylpolyamine coordinated to the copper. Since the rate generally increases with increasing basicity of the anionic species (Table II), a more plausible explanation is deprotonation of the coordinated amine (RNH_2) by the anion to give a more basic coordinated amido ligand (NHR^-).[20] However, a limited extent of deprotonation is evident from the fact that we find the rate of nitrocyclohexane reduction by cuprous acetate to be independent of excess acetate ion, at least up to a 2-mol excess. Deprotonation of coordinated amine has also been proposed previously in the copper(I)-catalyzed coupling of carbon monoxide and amines.[2]

Pressure–Temperature Effects.—While accurate rate measurements were not made at superatmospheric pressures of CO, generally it was found that the rate of nitroalkane reduction was insensitive to CO pressure, at least up to about 15 atm pressure. This is consistent with a high equilibrium concentration of copper(I) carbonyl. In eq 4, K is large,[1] and the equilibrium lies

$$Cu^+ + CO \overset{K}{\rightleftharpoons} Cu(CO)^+ \qquad (4)$$

well to the right under normal conditions. Furthermore, the rate of formation of $Cu(CO)^+$ is fast.[2] Increases in CO pressure should not have any significant effect upon the equilibrium concentration of $Cu(CO)^+$ species, and the rate of nitroalkane reduction should be independent of the carbon monoxide pressure. Some loss in rate has been noted at high pressures of CO (above 15 atm) where the formation of coordinatively saturated copper multicarbonyl species could become important.

An Arrhenius plot, showing the effect of temperature upon the nitrocyclohexane reduction rate, is reproduced in Figure 4. The straight-line plot is indicative of simple kinetics for this reaction over the temperature range studied (80–100°). From the gradient of the plot an experimental activation energy of 16.6 kcal mol^{-1} has been calculated.

Mechanism.—The results described above may be rationalized on the basis of Scheme I, where the initial reaction is the combination of the nitroalkane anion with the solvated copper(I) carbonyl, and this is followed by insertion of carbon monoxide into the copper–oxygen bond of the complex, cyclization, and cleavage, to yield the observed products. Consistent with our kinetic measurements, we believe the first step to be

(17) D. A. Johnson, "Some Thermodynamic Aspects of Inorganic Chemistry," Cambridge University Press, London, 1968, Chapter 4.

(18) S. Nakamura and J. Halpern, *J. Amer. Chem. Soc.*, **83**, 4102 (1961).

(19) "Stability Constants of Metal-Ion Complexes," Chemical Society Special Publication No. 17, 1964.

(20) G. W. Watt and J. F. Knifton, *Inorg. Chem.*, **7**, 1443 (1968).

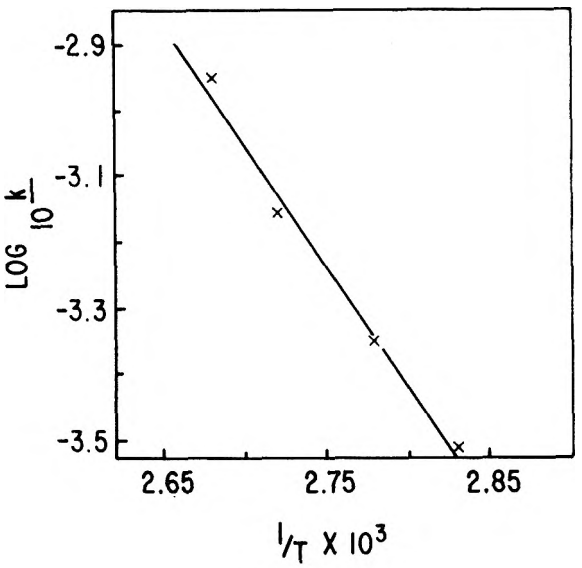
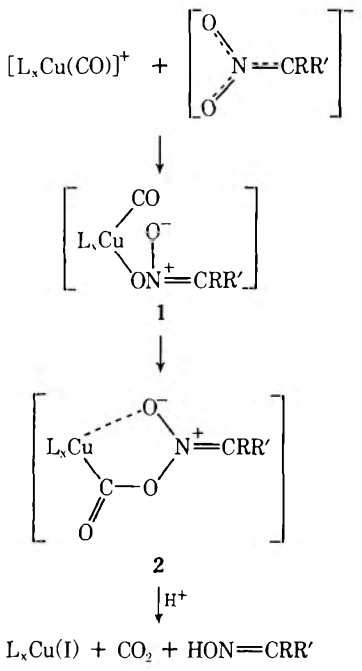


Figure 4.

SCHEME I[a]

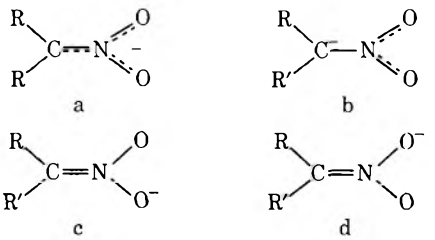


[a] L_x refers to coordinated amine.

slow and rate determining. The rate law is then of the form of eq 5.

$$\frac{-d[RNO_2]}{dt} = k[Cu][RNO_2^-] \quad (5)$$

Additional evidence for Scheme I, beyond that already cited, includes the following. First, while



nitroalkane anions might exist in four possible resonance forms, it has been concluded, from spectroscopic studies, that species a is normally present in the largest concentration.[21] Bonding of the nitroalkane anion with the copper(I) carbonyl in intermediate **1** is expected to be through the oxygens, rather than the carbon of the anion, by analogy with known metal nitroalkane compounds.[22]

The carbon monoxide insertion step to give intermediate **2** is an example of a well-documented class of reactions in organometallic chemistry involving insertion of unsaturated compounds, such as carbon monoxide, into metal–oxygen bonds. Pertinent examples include the CO insertion into copper–alkoxide[23] and copper–aquo bonds.[1]

Intermediate **2** is somewhat analogous to the labile nitronate esters (which may be prepared by the alkylation of primary or secondary nitroalkanes in basic media). These esters also undergo N–O bond fission to yield the corresponding aliphatic oximes.[24]

$$R_2C^+{=}N(O^-)OCH_2R' \longrightarrow R_2C{=}NOH + R'CHO \quad (6)$$

Catalysis by Silver Salts.—Although the CO molecule is relatively inert toward a variety of common oxidizing agents, it can be oxidized under mild conditions by a number of transition and posttransition metal ions.[7,18,25,26] Kinetic studies have shown that oxidation many times proceeds *via* a metal carbonyl intermediate formed by CO insertion into the metal–solvent bond;[7] while this may be followed by decomposition with oxidation of the CO to CO_2 and reduction of the metal, the reaction of these metal carbonyls with certain added oxidizing agents has been demonstrated.[27,28]

For the purpose of broadening the scope of the oxime synthesis, the catalytic activity of other metal carbonyls in amine solvents has been considered. It is reported[29] that silver nitroalkane complexes undergo spontaneous electron transfer to metallic silver and a dimer of the nitro anion. Here we find that CO-saturated solutions of silver salts in polyamines, such as ethylenediamine, will catalyze the reduction of nitroalkanes to oximes in moderate yields (see Table V). A comparison of the silver(I) catalyst with the analogous copper(I) system described above shows the following.

(a) A significant rate of oxime formation is achieved only at superatmospheric pressures of CO with the silver catalyst. Apparently the intermediate silver carbonyl is dissociatively less stable than the analogous copper(I) complex; *i.e.*, the equilibrium constant K in eq 4 is smaller for the Ag complex.

(b) The silver carbonyl is thermally less stable; consequently CO reduction experiments carried out at temperatures of 80° or above lead to the precipitation of silver metal, and a loss of catalyst activity.

(21) M. J. Brookes and N. Jonathan, *Spectrochim. Acta, Part A*, **25**, 187 (1969); A. H. Norbury, D. Sant, and P. E. Shaw, *J. Inorg. Nucl. Chem.*, **32**, 3401 (1970).

(22) A. C. Lee, *Spectrochim. Acta, Part A*, **28**, 133 (1972), and references cited therein.

(23) T. Saegusa, T. Tsuda, and K. Isayama, *J. Org. Chem.*, **35**, 2976 (1970)

(24) Reference 6, p 413.

(25) N. K. Eremenko and K. I. Matveev, *Kinet. Katal.*, **7**, 707 (1966); J. A. Stanko, G. Petrov, and C. K. Thomas, *Chem. Commun.*, 1100 (1969).

(26) B. R. James and G. L. Rempel, *Chem. Commun.*, 158 (1967).

(27) A. C. Harkness and J. Halpern, *J. Amer. Chem. Soc.*, **83**, 1258 (1961).

(28) A. B. Fasman and V. A. Goldor, *Dokl. Akad. Nauk SSSR*, **155**, 298 (1964).

(29) G. B. Brown and R. L. Shriner, *J. Org. Chem.*, **2**, 376 (1937).

TABLE V
ALIPHATIC OXIMES FROM NITROALKANES CATALYZED BY SILVER SALTS[a]

Silver salt	Nitroalkane	$[RNO_2]/[Ag]$	CO pressure, atm	Nitroalkane conversion, mol %	Oxime yield, mol %[b]
Silver acetate	Nitrododecane[c]	1	1	<2	None
Silver acetate	Nitrododecane	1	8	58	43
Silver acetate	Nitrododecane	1	36	73	56
Silver nitrate	Nitrododecane	1.5	72	64	*d*
Silver acetate	Nitrododecane	10	8	44	36
Silver acetate	Nitrocyclohexane	1.5	72	100	63

[a] Experimental conditions: solvent, 90% (v/v) ethylenediamine, 10% (v/v) water, 85°, 360 min. [b] Based on nitroalkane charged. [c] A mixture of 2- through 6-nitrododecanes. [d] Not determined.

(c) Highly basic alkylpolyamine solvents, such as ethylenediamine, are suitable for the CO reduction of nitroalkanes to oximes by silver salts. Carbonylation in the presence of primary and secondary monoamines is reported to yield *N,N'*-dialkylureas and *N,N,N',N'*-tetraalkyloxamides, respectively.[30]

Other metal ions known to activate molecular CO, including those of mercury(II), cobalt(II), manganese, and nickel, were also considered, but were found inactive for nitroalkane reduction over the range of conditions surveyed. This pattern of activity most likely reflects the relative lability and coordinative unsaturation of the intermediate metal carbonyls. The relatively stable carbonyls of copper(I) and silver(I) contrast with the analogous mercury complex,[27,31] which we find to rapidly dissociate to the metal in the presence of amine. The carbonyls formed from nickel(II) and cobalt salts in strongly basic media may be coordinately saturated, for example, nickel tetracarbonyl, prepared by the CO reduction of nickel salts in aqueous ammonia and 1,2-propanediamine.[32] They do not lend themselves, therefore, to attack by the nitroalkane anion under mild conditions.

Experimental Section

Carbon monoxide was Matheson C. P. grade. Ethylenediamine was distilled (bp 117–118°) and dried over molecular sieve. Other amine solvents were reagent-grade quality and were flushed wih CO prior to use. The copper(I) and copper(II) salts, 1-nitropropane, 2-nitropropane, nitrocyclohexane, and 1-nitroheptane were commercial products. Nitrododecane, a mixture of 2 through 6 isomers, was prepared by nitration of *n*-dodecane with nitrogen dioxide.

Synthesis Procedure.—The synthesis procedure for making aliphatic oximes is exemplified here for cyclohexanone oxime and dodecanone oximes, using solutions of copper(I) acetate in 1,3-propanediamine as catalyst. Oximes were also prepared with solutions of copper(II) salts; the procedure is similar except that a longer pretreatment with CO is required, to reduce the copper(II) to copper(I), prior to introducing the nitroalkane.

A. Synthesis of Cyclohexanone Oxime.—Copper(I) acetate (1.23 g, 10 mmol) was dissolved, with stirring, in a degassed sample of 1,3-propanediamine (200 ml) maintained at 85° under 1 atm pressure of carbon monoxide. The resulting solution was clear and pale yellow. Nitrocyclohexane (6.45 g, 50 mmol) was added slowly, and the mixture was stirred rapidly at 85° under CO for 2–4 hr. On cooling, the liquid product was concentrated *in vacuo*, diluted with water, and extracted with diethyl ether. The ethereal extracts were reconcentrated and the residual crude cyclohexanone oxime was recrystallized from aqueous ethanol. Cyclohexanone oxime yield was 4.55 g (81%), mp 90° (lit.[33] mp 91°). Identification was also by infrared[34] and nmr[35] spectroscopy and elemental analysis. *Anal.* Calcd for $C_6H_{10}NOH$: C, 63.7; H, 9.79; N, 12.4. Found: C, 63.8; H, 9.7; N, 12.3.

B. Preparation of Dodecanone Oximes.—Copper(I) acetate (2.46 g, 20 mmol) was dissolved, with stirring, in a solution of 1,3-propanediamine (180 ml) and water (20 ml) saturated with carbon monoxide at 85°. Nitrododecane, a mixture of 2 through 6 isomers (21.5 g, 100 mmol), was added slowly, and the whole was stirred rapidly at a temperature of 85° under CO for 3–4 hr. On cooling, the liquid product was concentrated and extracted with diethyl ether, and the ethereal extract was vacuum distilled. Dodecanone oximes, a mixture of 2 through 6 isomers, bp 126–128° (4 mm), with some decomposition [lit.[36] 6-dodecanone oxime, bp 147° (10 mm)], were obtained in 16.7-g (84%) yield. The oximes were identified by infrared,[34] nuclear magnetic resonance,[35] and mass spectrometry. *Anal.* Calcd for $C_{12}H_{24}NOH$: C, 72.3; H, 12.7; N, 7.02. Found: C, 72.2; H, 12.6; N, 7.02.

Kinetic Measurements.—Generally, only initial rates of nitroalkane reduction to oxime were determined in this work. Kinetic studies were carried out in glass apparatus set in a constant-temperature bath. Carbon monoxide was introduced *via* a fritted glass disk and stirring was by a Teflon paddle driven by a high-speed electric motor.

Degassed amine solvent (50 ml) and a weighed quantity of copper salt (0.25–2.50 mmol) were introduced into the 100-ml reaction flask and flushed with CO. Starting with copper(II) salts, the catalyst solution was stirred under CO until the color of the homogeneous solution changed from blue to pale yellow [*i.e.*, until all the copper(II) had been reduced to copper(I)]. There was no evidence of insoluble species either at this stage or after the addition of substrate. A known weight of nitroalkane (5.0–50 mmol) was introduced through a rubber septum, and the rate of reduction was monitored by withdrawing liquid samples (0.2 ml) at regular time periods. The samples were rapidly cooled in ice water and analyzed by gas chromatography with the aid of standard calibration curves. Chromatographic analysis was used to follow both the rate of disappearance of nitroalkane and the formation of oxime.

Rate studies with nitrododecane included *n*-dodecane as an internal standard. Experiments at superatmospheric pressures of CO involved a similar procedure but were carried out in a glass-lined pressure reactor of 300 ml rated capacity.

Acknowledgments.—The author wishes to thank Texaco Inc. for permission to publish this paper, Dr. I. Schwager for technical advice, and Messrs. T. S. Strothers and C. A. Dondero for experimental assistance.

Registry No.—Cyclohexanone oxime, 100-64-1; dodecanone oxime, 33940-11-3; nitrocyclohexane, 1122-60-7; nitrododecane, 27195-75-1.

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(32) E. Hirsch and L. Peters, *Can. Met. Quart.*, **3**, 137 (1964).
(33) W. Huckel and M. Sachs, *Justus Liebigs Ann. Chem.*, **498**, 166 (1932).
(34) H. E. Ungnade, G. Fritz, and L. W. Kissinger, *Tetrahedron, Suppl. 1*, **19**, 235 (1963); J. F. Brown, *J. Amer. Chem. Soc.*, **77**, 6341 (1955).
(35) G. J. Karabatsos and R. A. Taller, *Tetrahedron*, **24**, 3347 (1968).
(36) L. Bouveault and R. Locquin, *C. R. Acad. Sci.*, **140**, 1699 (1905).

Chemical Evolution. XIV. Oxidation of Diaminomaleonitrile and Its Possible Role in Hydrogen Cyanide Oligomerization[1]

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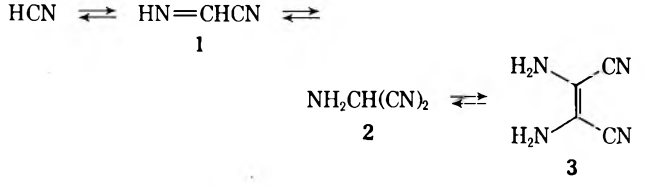
Received June 4, 1973

N,N'-Diisopropyldiaminomaleonitrile (**4**) is oxidized by oxygen to *N,N'*-diisopropyldiiminosuccinonitrile (**5**) in 47% yield in acetonitrile solution. The yield of **5** is much less in aqueous solution at pH 9.2 with monoisopropylurea as the other reaction product. Ammoniacal hydrolysis of **5** (0.1 mmol) gives urea (0.076 mmol) as the only reaction product, while hydrolysis in the presence of a 30-fold excess of cyanide gives an enhanced yield of urea (0.28 mmol). These results may be explained by the reduction of **5** to **4** by cyanide with the subsequent formation of cyanogen or cyanate which in turn reacts with ammonia to give urea. Oxygen oxidizes **4** to **5**, thus completing the cycle. Diaminomaleonitrile (**3**) is air oxidized in aqueous ammonia (pH 9.2) and urea was detected as a reaction product. Diiminosuccinonitrile (**6**) is the most likely initial oxidation product of **3**. A 50% yield of urea is obtained on hydrolysis of **6** in ammonical solution. However, this yield did not increase when the hydrolysis was performed in the presence of cyanide. A pH 9.2 solution of cyanide in the presence of oxygen decomposes more rapidly than one which has been degassed. The detection of urea and amino acids (after acid hydrolysis) from the degassed cyanide solution demonstrates that oxidation and reduction leading to urea and the amino acid precursors are taking place in the absence of oxygen, suggesting that these reactions were feasible on the primitive earth.

HCN condenses in aqueous alkaline solution to yield a variety of biomolecules, or their precursors, including purines,[2a] amino acids,[2b] and pyrimidines.[2c] These findings, together with the ease with which HCN is formed in primitive earth simulation experiments,[3,4] suggest that HCN condensation reactions may have been an important source of biomolecules on the primitive earth.

The condensation of HCN to diaminomaleonitrile (HCN tetramer, **3**) is well understood.[3,5] The reaction proceeds *via* the stepwise formation of dimer **1**, trimer **2**, and **3**. On further reaction the concentra-



tion of **3** gradually decreases and the so-called "HCN polymer" forms.[6,7] Amino acids have been identified among the acid hydrolysis products of this material.[2b] Substantial amounts of urea, together with oxalic acid, are also produced in the oligomerization mixture.[2b,7,8] These compounds must be formed by oxidation–reduction processes, because urea and oxalic acid are oxidation products of HCN while amino acids represent reduction products.

3 and to a lesser extent adenine are the highest molecular weight oligomers of HCN to be isolated and characterized from the oligomerization of dilute (0.1–1.0 *M*) aqueous cyanide.[2a,9] The apparent absence of higher oligomers suggests that the redox reactions leading to urea, oxalic acid, and the other substances found in the oligomerization mixture[8] involve compounds **1**, **2**, and **3**. The rapid conversion of **1** and **2** to **3** in the presence of cyanide suggested **3** to be the most likely candidate for oxidation and/or reduction.[3,5] The possible loss of **3** due to the facile oxidation or reduction of the low equilibrium concentrations of **1** or **2** cannot be excluded as a possibility.

Several lines of evidence suggested that cyanate was the direct precursor to urea in the oligomerization mixture.[7] First, much more urea is obtained when the oligomerization is performed in the presence of ammonium hydroxide than is formed at the same pH in the absence of ammonia hydroxide. Furthermore, *N*-methylurea is the product, instead of urea, when the oligomerization is performed in the presence of methylamine. Finally, carbamyl derivatives of amino acids have been detected as hydrolysis products of the "HCN polymer."[2c,7]

In the present work, the reactions of **3** and the dialkyl substituted derivatives of **3** were investigated with the aim of delineating which redox reactions are occurring during the HCN oligomerization.

Results

Reactions of *N,N'*-Diisopropyldiaminomaleonitrile and *N,N'*-Diisopropyldiiminosuccinonitrile.—A study of the solution chemistry of *N,N'*-diisopropyldiaminomaleonitrile[5] (**4**) was undertaken with the expectation that isopropyl groupings would facilitate product isolation and analysis. Compound **4** was found to be unstable in aqueous solution at pH 9.2. Its absorption maximum at 332 nm disappeared in 2–4 hr while the short-wavelength band at about 222 nm increased slightly. After standing for several days the 222-nm band disappeared and a band at 206 nm formed.

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(8) The term "oligomerization mixture" will be defined as in ref 7 to describe the complex mixture of reaction products formed from HCN. This term refers not only to the primary reaction products (**1**–**3**) which are true oligomers but also to the other products formed by oxidation, reduction and hydrolysis of these primary oligomeric species.[7]

(9) Adenine (HCN pentamer) has been isolated from more concentrated cyanide solutions.[2a]

Monoisopropylurea was isolated as a reaction product at the end of this time.

The rate of decomposition of **4** is independent of the concentration of added cyanide or isopropylamine but increased with increasing pH. The formation of monoisopropylurea is not inhibited by the addition of nucleophiles such as iodide or cyanide to the reaction solution. Monoisopropylurea was detected as a reaction product when the hydrolysis of *N,N'*-diisopropyldiaminomaleonitrile was performed in aqueous isopropylamine. It was not possible to ascertain if *N,N'*-diisopropylurea was a reaction product because we did not have a sensitive method for its detection. Thus, the loss of **4** apparently is not caused by the attack of a nucleophile, such as an amine or cyanide, on **4** or by the decomposition of a lower molecular weight oligomer in equilibrium with **4**. If nucleophilic attack were important the added nucleophiles should accelerate the decomposition of **4**, while the presence of cyanide would be expected to displace the equilibrium between a lower oligomer and **4** in the direction of **4**. This should slow the rate of decomposition of the lower molecular weight oligomer.

That the decomposition of **4** was due to atmospheric oxygen was demonstrated by comparing the rate of loss of **4** in degassed and nondegassed solutions. The uv maximum of **4** at 322 nm decreased only slightly in 8 hr in the degassed solution, while it disappeared in 40 min in the nondegassed solution.

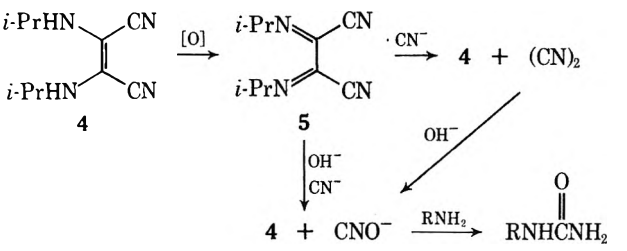
When the maleonitrile **4** was oxidized in acetonitrile, diisopropyldiiminosuccinonitrile (**5**) was isolated in 47% yield. The structure of **5** was assigned by comparison of its uv spectrum with that reported for *N,N*-di-*tert*-ocyldiiminosuccinonitrile.[10] The uv spectrum of **5** exhibits an intense maximum at 230 nm (ϵ 1.76 × 10^4) at about the same wavelength as the short-wavelength maximum of **4** [226.5 nm (ϵ 1.3 × 10^4)] as well as a weak maximum at 306 nm (ϵ 365). The decrease in the intensity of the uv maximum of **4** at 332 nm and the small variation in the spectrum at 225 nm is consistent with the oxidation of **4** to **5** in aqueous solution. It was also possible to isolate **5** as a reaction product when the oxidation was performed in aqueous medium.

Since we established **5** to be the oxidation product of **4** we then investigated the hydrolysis of **5** in ammoniacal solution at pH 9.2. Only urea could be detected as a reaction product and no isopropylurea was evident. The absence of isopropylurea was established by paper chromatography and by an independent color reaction which can be used to distinguish urea from monosubstituted ureas.[11] Therefore, urea formation from **5** must involve either (1) decomposition of **5** to a derivative which does not contain the isopropyl grouping, which in turn reacts with ammonia to give urea; (2) reaction of ammonia with diiminosuccinonitrile in such a way (*e.g.*, at the nitrile grouping) to give urea and no isopropylurea; (3) reaction of **5** with some other substance (*e.g.*, cyanide) to give a compound which yields urea on further reaction.

That alternate 3 above was the pathway for urea synthesis was established by performing the hydrolysis of **5** in the presence of cyanide. When the ammoniacal hydrolysis of 0.1 mmol of **5** was performed in the absence of cyanide 0.076 mmol of urea was produced. When the same reaction was performed in the presence of a 30-fold excess of cyanide, 0.28 mmol of urea was obtained.[12] Although urea is produced by the direct reaction of cyanide and ammonia, it will be shown later that its rate of synthesis is much slower than was observed in these experiments.

A plausible explanation for these data is given in Scheme I. In the presence of added cyanide ion **5**

SCHEME I



oxidizes the cyanide ion to cyanogen[13a] or cyanate.[13b] The cyanogen is cleaved by base to give cyanide and cyanate.[13a] The cyanate reacts with ammonia or amines to give the corresponding urea. More than 1 equiv of urea is obtained in this process because **4**, the reduction product of **5**, is readily air oxidized to **5** and the redox cycle can begin again. A small yield of monoisopropylurea is obtained in the absence of ammonia because the requisite cyanide and isopropylamine are formed in small amounts by the hydrolytic decomposition of **5**. In the presence of added ammonia (but no added cyanide) the isopropylamine is swamped out by the ammonia and urea is the reaction product.

Reactions of Diaminomaleonitrile (3) and Diiminosuccinonitrile (6).—The decomposition of **3** in aqueous pH 9.2 ammonia proceeds more rapidly in the presence of air and oxygen than when the solution is degassed (Table I). The formation of urea parallels the de-

TABLE I

OXIDATION AND HYDROLYSIS OF DIAMINOMALEONITRILE (**3**)

	1[a]		2[b]		3[c]		4[d]	
Time, days	**3**,[e] $M \times 10^4$	Urea,[f] $M \times 10^4$	**3**,[e] $M \times 10^4$	Urea,[f] $M \times 10^4$	**3**,[e] $M \times 10^4$	Urea,[f] $M \times 10^4$	**3**,[e] $M \times 10^4$	Urea,[f] $M \times 10^4$
0	93		93		93		93	
1	91							
2	89		40		22			
3	78	12						
4	61	21						
5	57		11		4		90	
6	46	27						
9			0	125	0	156		
13							82	
43							63	
76–82			0	110	0	99	46	0

[a] Open to the atmosphere. [b] Three freeze–pump–thaw cycles and opened to the atmosphere. [c] Three freeze–pump–thaw cycles and an oxygen atmosphere added. [d] Three freeze—pump–thaw cycles and sealed *in vacuo* in separate ampoules. One ampoule opened on each indicated day. [e] **3** measured from uv maxima at 295 nm.[3] [f] Determined by procedure of Ormsby.[11]

(10) L. deVries, *J. Org. Chem.*, **36**, 3442 (1971).
(11) A. Ormsby, *J. Biol. Chem.*, **146**, 595 (1942).

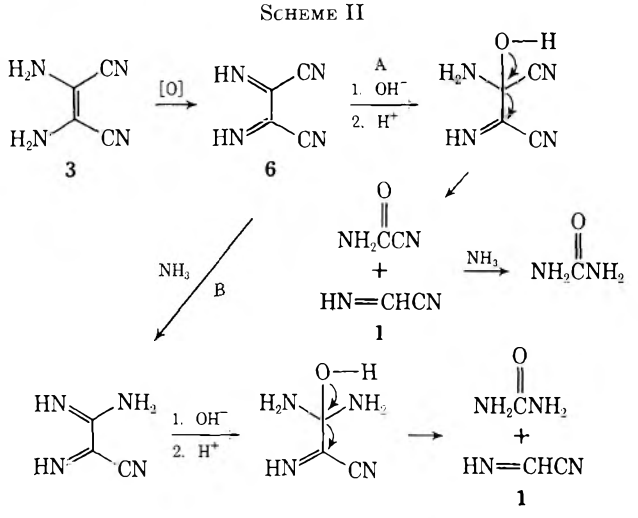
(12) The urea yields given in the Experimental Section were normalized here to those that would be obtained from 0.1 mmol of **5**.
(13) (a) K. Brotherton and J. W. Lynn, *Chem. Rev.*, **59**, 841 (1959); (b) W. M. Latimer, "Oxidation Potentials," Prentice-Hall, Englewood Cliffs, N. J., 1952, p 50.

composition of **3** (Table I) except in the degassed solution. There, no urea could be detected even after 76 days, when 50% of **3** had decomposed. The molar ratio of urea formed to the initial concentration of **3** was 1.35–1.7 after 9 days. This ratio was somewhat less after about 80 days, probably owing to the slow hydrolysis of the urea.

A 50% yield of urea is obtained on hydrolysis of **6** in a pH 9.3 aqueous ammoniacal solution, suggesting that **6** is the initial oxidation product of **3**. **6** has been obtained as the oxidation product of **3** in nonhydroxylic solvents.[14] Isopropylurea was obtained when the hydrolysis was carried out in the presence of isopropylamine. In contrast to the findings with *N*,*N*-diisopropyldiiminosuccinonitrile, the yield of urea did not increase when the hydrolysis of **6** was performed in the presence of a sixfold excess of cyanide. This difference between **6** and *N*,*N*′-diisopropyldiiminosuccinonitrile reflects the more rapid hydrolysis of **6**. It was impossible to detect **6** in a pH 9.2 reaction mixture after 13 hr while the disubstituted diiminosuccinonitrile (**5**) can be isolated from a 3-day air oxidation of **4** in aqueous solution. Apparently the reduction of **5** by cyanide is slower than the hydrolysis of **5**.

These experiments establish that urea must be formed directly from **6**. Two possible pathways are shown in Scheme II. Paths A and B differ only in

SCHEME II



the timing of the addition of hydroxide ion and ammonia to **6** respectively. These addition reactions are similar to those proposed for the addition of amines to **6** in nonpolar solvents.[14] The cleavage of **6** by base (path A) is similar to the cleavage of cyanogen to cyanate and cyanide by base[13a] and the hydrolysis of **3** to aminoacetonitrile.[3] Iminoacetonitrile (**1**) can serve as a leaving group because the negative charge is stabilized by the sp^2 carbon atom and the proximate cyano group.

The possibility that aminomalononitrile (**2**), in equilibrium with **4**, is the direct precurser to urea was eliminated by the following experiments. A fivefold excess of cyanide was added to an ammoniacal solution of **2** with the final pH 9.3. A 52% yield of **3** was observed after 10 min; however, no urea could be detected. A 19% yield of urea was detected after 2 days, a result consistent with the initial formation of **3** followed by the formation of urea.

Oligomerization of HCN.—Urea is produced in the HCN oligomerization mixture and the corresponding monosubstituted urea is formed when an organic amine is added to the reaction mixture.[7] In the present work we found that urea is formed slowly during the oligomerization of cyanide. No urea could be detected from 0.1 *M* cyanide after 20 days, and a 1.2% yield (based on initial cyanide) was detected after 83 days. A 5% yield (7% based on cyanide consumed) was obtained after 14 months. Urea is slowly hydrolyzing under the reaction conditions; so the actual amount formed is greater than 7%. Since **3** is readily oxidized, the effect of oxygen on the oligomerization of cyanide was then investigated. A portion of a stock solution of *ca.* 0.15 *M* cyanide was degassed by four freeze–pump–thaw cycles and then sealed under vacuum while the other portion was allowed to stand open to the atmosphere. Both solutions darkened at about the same rate. Analysis of the nondegassed solution after 1 month indicated that it was 0.135 *M* in cyanide.[15] After 7 months the degassed solution was 0.053 *M* in cyanide while the nondegassed was 0.024 *M*. The degassed solution was 1.9×10^{-3} *M* in urea after 7 months while the nondegassed solution was 3.7×10^{-3} *M* in urea. These data indicate that the same redox reactions are occurring in the presence and absence of oxygen. Further confirmation of this conclusion was obtained by the acid hydrolysis of the oligomerization mixture formed in the degassed and nondegassed cyanide solutions. Paper chromatography with ninhydrin spray indicated that the same amino acids were released in each instance.[16]

Conclusions

3 and the dialkyl-substituted derivatives of **3** are readily oxidized by molecular oxygen to the corresponding **6** derivatives.[9,10] Hydrolysis of **6** in the presence of ammonia yields urea. Since **3** is formed in significant amounts in the oligomerization of cyanide, one might expect that the presence of oxygen might exert a significant effect on this reaction. However, the oligomerization proceeds equally as well in the presence or absence of oxygen. The rate of cyanide loss is considerably less in the absence of oxygen; however, urea is produced in the oligomerization mixture on acid hydrolysis. Since redox steps must be involved in the formation of these compounds, either some other cyanide oligomers must be effecting these oxidation reactions or disproportionation reactions are occurring. The formation of amino acids and other biomolecules from HCN could have occurred on the primitive earth in the absence of oxygen.

The ease of oxidation of **3** suggests that it is being oxidized by other cyanide oligomers in the absence

(14) The reduction of diiminosuccinonitrile to diaminomaleonitrile in organic solvents by cyanide and the resulting formation of cyanogen has been reported: R. W. Begland, A. Cairncross, D. S. Donald, D. R. Hartter, W. A. Sheppard, and O. W. Webster, *J. Amer. Chem. Soc.*, **93**, 4953 (1971); O. W. Webster, D. R. Hartter, R. W. Begland, W. A. Sheppard, and A. Cairncross, *J. Org. Chem.*, **37**, 4133 (1972).

(15) A. A. Schilt, *Anal. Chem.*, **30**, 1409 (1958). This procedure was modified as described in ref 3.

(16) Similar results have been obtained in this laboratory by Drs. J. D. Wos and J. Wittmann.

of oxygen.[17] One pathway to the urea produced during the cyanide oligomerization is by the hydrolysis of 6. The ease with which cyanide is oxidized to cyanate and cyanogen[13] in basic medium suggests that urea and oxalate may be formed by these routes as well.[7]

Experimental Section[18]

Materials.—Isopropylurea was prepared by the reaction of isopropylamine with KCNO, mp 148–152° (lit.[21] mp 154°), ir identical with that of a published spectrum.[22] Diisopropylurea was prepared by the reaction of phosgene with isopropylamine, mp 187–189° (lit.[23] mp 192°). Diiminosuccinonitrile was supplied by Dr. W. A. Sheppard of E. I. du Pont. **3**, *N,N'*-Diisopropyldiaminomaleonitrile,[5] and aminomaloninitrile *p*-toluenesulfonate[24] were prepared as described previously.

Quantitative Analysis for Urea.—The method of Ormsby[11] was modified in a few minor respects. The final volume of the solution after addition of potassium persulfate was made up to either 10 or 25 ml. The solution was then placed in a uv cell and the absorbance recorded with time. The maximum absorbance was used as the value for the determination. Standards were run simultaneously with the unknown sample.

Decomposition of *N,N'*-Diisopropyldiaminomaleonitrile in Aqueous Sodium Cyanide Solution.—A solution of sodium cyanide (117.3 mg, 2.4 mmol) and *N,N'*-diisopropyldiaminomaleonitrile[5] (8.6 mg, 0.05 mmol) in 10 ml of ethanol–water (1:1) was made up as a stock solution (solution A). A portion (2 ml) of solution A was diluted to 100 ml using ethanol–water (1:1) (solution B). A portion (2 ml) of solution A was diluted to 10 ml using ethanol–water (1:1) (solution C). The uv spectrum of the most dilute solution was followed initially and the more concentrated solutions were monitored in the later stages of the decomposition.

Over a period of 3 hr, there was a decrease in the absorption at 332 nm and an increase in the absorption at 222 nm. After 1 hr, the absorbance at 222 nm began to decrease. After 6 days, the maximum of 222 nm disappeared, and a maximum of 206 nm appeared. There was a continuum of absorption to above 400 nm. The solutions were combined and the solvent was removed on a rotary evaporator to yield a brown-yellow solid residue. The residue was washed well with chloroform, the chloroform washings were combined, and the solvent was removed on a rotary evaporator. The presence of monoisopropylurea in the chloroform extract was established by paper chromatography (BAW) (R_f 0.83) followed by spraying with Ehrlich's reagent.

Decomposition of *N,N'*-Diisopropyldiaminomaleonitrile in Degassed and Nondegassed Aqueous Sodium Cyanide Solutions.—*N,N'*-Diisopropyldiaminomaleonitrile (2.4 mg) was dissolved in ethanol–water (1:1) (100 ml) to make a stock solution. The reaction vessel consisted of a Pyrex cell and a quartz cell at a 90° angle. These cells were part of one apparatus which could be outgassed on a vacuum line.

A.—Sodium cyanide (10.0 mg, solid) was placed in the quartz cell. A portion (*ca.* 3 ml) of the above solution was placed in the Pyrex cell and degassed by four freeze–pump–thaw cycles. The stopcock was then closed to maintain the system under vacuum.

B.—Sodium cyanide (29.8 mg. solid) was placed in the quartz cell. A portion (*ca.* 3 ml) of the stock solution was placed in the Pyrex cell. The solution was then carried through four freeze-thaw-cycles *without* degassing.

After degassing or simulated degassing the solutions in the Pyrex cells were then poured into the quartz cells containing the solid sodium cyanide and shaken to cause the sodium cyanide to dissolve. The uv spectra were recorded over a period of time. After 40 min, the absorbance at 332 nm (*N,N'*-diisopropyldiaminomaleonitrile) had disappeared for solution B (not degassed). This was a loss of 1.4 absorbance units. There was a loss of only 0.14 absorbance units in solution A during this time. The small loss in solution A may have been due to residual oxygen not removed in degassing. Consistent with this is the observation that after 8 hr, solution A had only lost 0.18 absorbance units. After 22.5 hr, solution A had lost 0.56 absorbance uuits (this loss on long standing may be due to slow leakage at the stopcock). The stopcock was then opened to allow air into the cell. Within 2 hr, all the absorbance at 332 nm has disappeared (loss of 0.94 absorbance units).

Decomposition of *N,N'*-Diisopropyldiaminomaleonitrile in the Presence of Nucleophiles Other Than Cyanide Ion.—A stock solution of *N,N'*-diisopropyldiaminomaleonitrile (57.6 mg, 0.3 mmol) in ethanol–water (10 ml, 1:1) was prepared. Two solutions were made up from this stock solution.

A.—A solution of *N,N'*-diisopropyldiaminomaleonitrile (11.3 mg, 2 ml of stock solution) and sodium iodide (345.8 mg, 2.32 mmol) was made up to 10 ml with ethanol–water (1:1).

B.—A solution of *N,N'*-diisopropyldiaminomaleonitrile (11.3 mg, 2 ml of stock solution) was made up to 10 ml with ethanol–water (1:1). The final pH of this solution was adjusted to 9.74 with 10% sodium hydroxide and 10% hydrochloric acid.

Analysis of the solutions after 6 days by paper chromatography (BAW, Ehrlich's reagent) indicated that there was monoisopropylurea in solution B not in solution A. After 25 days, solution B gave a weak positive test for cyanide ion.[15] Iodide ion interferes with this test, so that solution A could not be analyzed.

Conversion of *N,N'*-Diisopropyldiaminomaleonitrile to *N,N'*-Diisopropyldiminosuccinonitrile in Acetonitrile in the Presence of Anhydrous Sodium Carbonate.—*N,N'*-Diisopropyldiaminomaleonitrile (57.4 mg, 0.30 mmol) was dissolved in acetonitrile (10 ml). Anhydrous sodium carbonate (194.6 mg, 1.83 mmol) was added and the mixture was stirred at room temperature overnight. The sodium carbonate was removed by filtration. The acetonitrile was removed on a rotary evaporator to yield 53.4 mg of a white solid, mp 92–97°. After sublimation [40° (0.6 Torr)] a white solid, mp 98–99°, 27.1 mg (47%), was obtained. This was identified as *N,N'*-diisopropyldiminosuccinonitrile on the basis of its spectra: ir (KBr) 3012, 2933, 2230 (w, C≡N), 1618 (C=N), 1451, 1370, 1350, and 1163 cm^{-1}; uv max (CH_3CN) 306 nm (δ 365), 230 (1.76×10^1); nmr (CCl_4) δ 1.35 (d, J = 3 Hz, 6.8 H), 4.15 (septet, only five peaks resolved, 1 H); mass spectrum *m/e* (rel intensity) 190 (0.5), 175 (4), 133 (25), 96 (14), 95 (6), 76 (3), 55 (5), 54 (16), 43 (100), 42 (15), 41 (36), 40 (6), 39 (18), 27 (35).

Anal. Calcd for $C_{10}H_{14}N_4$: C, 63.16; H, 7.37. Found: C, 63.14; H, 7.46.

Decomposition of *N,N'*-Diisopropyldiaminomaleonitrile in Aqueous Isopropylamine.—Isopropylamine (4.1 ml, 48 mmol) was dissolved in water (10 ml) and the pH of the solution was adjusted to 9.2 using 10% HCl. The final volume was about 45 ml. A portion of this solution (20 ml, *ca.* 20 mmol) was placed in a 50-ml erlenmeyer flask and *N,N'*-diisopropyldiaminomaleonitrile (25.1 mg, 0.13 mmol) was added. Ethanol (95%, 5 ml) was added to bring the *N,N'*-diisopropyldiaminomaleonitrile into solution. After 3 days, the solution had turned yellow and fine white needles precipitated. The solution and needles were extracted with ether (2 × 25 ml). The ether extracts were combined and dried over anhydrous sodium sulfate. Tlc (silica gel–$CHCl_3$) gave two spots, one with an R_f corresponding

(17) Diaminosuccinic acid is one of the major amino acids produced by hydrolyses of the oligomerization mixture (J. D. Wos, unpublished). This result suggests that diaminomaleonitrile may also be serving as an oxidizing agent, although other explanations are also possible.

(18) The infrared spectral data were recorded on a Perkin-Elmer Model 137 sodium chloride spectrophotometer. The nmr spectra of solutions in deuteriochloroform, with TMS as an internal standard, were recorded on a Varian Model T-60 spectrometer. Ultraviolet spectra were recorded on a Unicam Model SP 800A spectrophotometer. Mass spectra were obtained using a Hitachi Perkin-Elmer RMU-6E mass spectrometer. pH measurements were made on a Radiometer Model 26 pH meter equipped with Corning 476050 electrode. Elemental analyses were carried out at Instranal Laboratory Inc., Rensselaer, N. Y. Melting points are uncorrected. Paper chromatography was by ascending development on Whatman 3MM at room temperature for *ca.* 15 hr. Abbreviations used: BAW, 1-butanol–acetic acid–water 5:2:3; BW, 1-butanol saturated with water; PA, 1-propanol–14.8 *M* ammonium hydroxide 3:1. Ehrlich's reagent[19] and Folin's reagent[20] were used as visualizing reagents. Compounds were visualized at 254 nm light source in all cases where a spray reagent was not used. Diaminomaleonitrile was estimated by its uv absorption at 295 nm (ϵ 1.35×10^4).[3]

(19) R. A. Heacock and N. E. Mahon, *J. Chromatogr.*, **17**, 338 (1965).

(20) I. M. Hais and K. Macek, "Paper Chromatography," Publishing House of Czechoslovak Academy of Sciences, Prague, 1963, p 809.

(21) Beilstein's "Handbuch der Organischen Chemie," 4th ed, Bd IV, J. Springer, Berlin, 1937, p 154.

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(23) T. Mukaryama and Y. Fujita, *Bull. Chem. Soc. Jap.*, **29**, 54 (1956).

(24) J. P. Ferris, R. A. Sanchez, and R. W. Mancuso, *Org. Syn.*, **48**, 1 (1968).

to *N,N'*-diisopropyldiiminosuccinonitrile. When the ether was stripped off and the residue was placed in a sublimator [room temperature (0.5 Torr)], a small amount of a white solid, mp 88–91°, sublimed. The infrared spectrum of this material was identical with that of *N,N'*-diisopropyldiiminosuccinonitrile, mp 98–99°.

Analysis of the water layer by paper chromatography using BAW gave a faint spot corresponding to isopropylurea when the paper was sprayed with Ehrlich's reagent.

Reaction of Isopropylamine with *N,N'*-Diisopropyldiaminomaleonitrile.—Isopropylamine (4.1 ml, *ca.* 48 mmol) was dissolved in 10 ml of water and the pH was adjusted to 9.16 with 25% hydrochloric acid. The final volume was about 35 ml. *N,N'*-Diisopropyldiaminomaleonitrile (23.0 mg, 0.12 mmol) was dissolved in 95% ethanol (7 ml) and added to the isopropylamine solution. The solution was allowed to stand at room temperature protected from room light. After 5 months, paper chromatography using BAW and Ehrlich's reagent showed the presence of monoisopropylurea. It was difficult to determine whether any *N,N'*-diisopropylurea had been formed. *N,N'*-diisopropylurea would be expected to be insoluble but no precipitate was observed. On paper chromatography using BAW and iodine vapors, it was difficult to get a good development of the spot for the authentic *N,N'*-diisopropylurea; so it was not certain if it was formed.

Decomposition of *N,N'*-Diisopropyldiiminosuccinonitrile in Aqueous Ammonia.—A portion (3.0 ml) of 14.8 *M* ammonium hydroxide solution was diluted to 10 ml with water. The solution contained about 45 mmol of ammonium hydroxide. The pH of the solution was adjusted to 9.2 with 10% hydrochloric acid. The final volume was about 35 ml. *N,N'*-Diisopropyldiiminosuccinonitrile (20.7 mg, 0.11 mmol) was added to this solution along with ethanol (15 ml). All the solid did not dissolve. The volume of the solution was made up to 50 ml with distilled water, and the solution was allowed to stand at room temperature protected from room light. After 43 days, analysis[11] indicated that it contained 5 mg (0.084 mmol) of urea. The presence of urea was confirmed by paper chromatography using BAW and Ehrlich's spray.

Decomposition of *N,N'*-Diisopropyldiiminosuccinonitrile in Aqueous Ammonia in the Presence of Cyanide.—A portion (3.0 ml) of 14.8 *M* ammonium hydroxide solution was diluted to 10 ml with water. The pH of the solution was adjusted to 9.2 with 10% hydrochloric acid. The final volume of the solution was about 35 ml. Potassium cyanide (355.9 mg, 5.5 mmol) was added to the solution and it dissolved completely. Diisopropyldiiminosuccinonitrile (35.4 mg, 0.19 mmol, mp 93–97°) was added to the solution along with ethanol (15 ml) in an attempt to solubilize the diisopropyldiiminosuccinonitrile. This was only partially successful and some solid remained undissolved. The volume of the solution was made up to 50 ml with distilled water and the solution was allowed to stand at room temperature, protected from room light. The solution contained 32 mg (0.53 mmol) of urea[11] and essentially no isopropylurea after 42 days.[11] We verified that both urea and isopropylurea can be distinguished by this procedure. Paper chromatography using BAW and spraying with Ehrlich's reagent confirmed the presence of urea.

Decomposition of Diaminomaleonitrile in Aqueous Ammonia.—A solution of ammonium hydroxide (296 mmol) was neutralized to pH 9.2 with 50% HCl and diluted to 200 ml in a volumetric flask. Diaminomaleonitrile (200 mg, 1.85 mmol) was added to this stock solution. A portion of this stock solution was left open to the atmosphere. A portion was carried through three freeze–pump–thaw cycles and then opened to the atmosphere. A 25-ml portion was degassed by three freeze–pump–thaw cycles and then sealed in the presence of 1 atm of pure oxygen. Portions (5 ml) were placed in bulbs, degassed by three freeze–pump–thaw cycles, and sealed under vacuum. The solutions were analyzed for diaminomaleonitrile and urea and the results are given in Table I.

Quantitative Analysis of the Amount of Urea and Cyanide Formed from Diiminosuccinonitrile in Aqueous Ammonia.—Ammonium hydroxide (3 ml of 14.8 *M* solution) was diluted to 10 ml with distilled water and the pH was then adjusted to 9.26 with 10% hydrochloric acid solution. The final volume was about 35 ml. Diiminosuccinonitrile (125.2 mg, 1.18 mmol) was dissolved in this solution and allowed to stand at room temperature for 1.5 months protected from light. Analysis by paper chromatography using BAW and Ehrlich's reagent indicated that there was urea present in the solution. The solution was filtered, diluted to 50 ml in a volumetric flask, and then analyzed for cyanide[15] and for urea.[11] These analyses indicated that the solution contained 1.34 mmol of cyanide and 0.53 mmol of urea.

Decomposition of Diiminosuccinonitrile in Aqueous Ammonia in the Presence of Excess Cyanide Ion.—A 35-ml solution containing 45 mmol of NH_4OH and 5.4 mmol of KCN was neutralized to pH 9.2 with 10% HCl and 0.9 mmol of diiminosuccinonitrile was added to it. After 16 days, a brown precipitate was removed by filtration and the filtrate was made up to 50 ml with distilled water. Analysis of the solution indicated that it contained 28 mg (0.46 mmol) of urea.[11] After 82 days, analysis indicated 31.1 mg (0.52 mmol) of urea. The presence of urea was confirmed by paper chromatography using BAW and Ehrlich's reagent.

Decomposition of Diiminosuccinonitrile in Aqueous Isopropylamine Solution.—Isopropylamine (4.1 ml, *ca.* 48 mmol) was dissolved in 10 ml of water and the pH of the solution was adjusted to 9.2 with 10% hydrochloric acid solution. The final volume was about 45 ml. Diiminosuccinonitrile (45.2 mg, 0.42 mmol) was dissolved in 20 ml of this solution. The solution was allowed to stand at room temperature for 3 days, at which time the solution was red brown in color and a black precipitate had formed. Analysis by tlc (silica gel–ethyl acetate) showed no starting material. Tlc [silica gel, chloroform–ethanol (1:1)] showed a spot corresponding to isopropylurea (R_f 0.85) when the plate was sprayed with Ehrlich's reagent. Paper chromatography (using BAW and spraying with Ehrlich's reagent) confirmed the presence of isopropylurea. There was no evidence for the presence of urea on tlc or paper chromatography.

Reaction of Aminomalononitrile with Cyanide Ion.—A portion (3.0 ml) of 14.8 *M* ammonium hydroxide was diluted with distilled water, and the pH was adjusted to 9.3 with 10% hydrochloric acid, giving a final volume of 35 ml. Aminomalononitrile *p*-toluenesulfonate (100 mg, 0.39 mmol) and KCN (137 mg, 2 mmol) were added and the solution turned yellow. The solution was made up to 50 ml in a volumetric flask using distilled water. The pH was 9.34. A uv spectrum measured 10 min after the start of the reaction indicated that the solution contained diaminomaleonitrile (4.00×10^{-3} *M*, 52%). No urea could be detected when a 1 ml aliquot of the stock solution was analyzed for urea.[11] A concentration of 0.05 mg/ml could have been detected. Urea could be detected after 1 month by paper chromatography using BAW and Ehrlich's spray.

In a repeat of this experiment, the ammonium hydroxide solution was made up as above and the pH was adjusted to 9.23. Aminomalononitrile (100.4 mg, 0.39 mmol) and potassium cyanide (132.7 mg, 1.9 mmol) were dissolved in the ammonium hydroxide solution. After 2 hr, a 59% yield of diaminomaleonitrile was obtained. After 2 days, the reaction solution contained 4.5 mg (0.075 mmol) (19%) of urea.[11] After 1 month the presence of urea was confirmed by paper chromatography using BAW and Ehrlich's reagent.

Analysis of HCN Oligomerization Solutions for Cyanide and Urea. A.—A solution of 0.103 *M* HCN in water was adjusted to 9.2 with ammonium hydroxide. After 14 months, the solution was analyzed for urea[11] and cyanide ion.[11] These analyses indicated that the solution was 0.03 *N* in cyanide ion (about 70% of cyanide gone) and 0.0053 *M* in urea (about 7% based on cyanide lost).

B.—A 50 ml solution containing 3 ml of 14.5 *M* NH_4OH and 361 mg (5.6 mmol) of KCN was adjusted to pH 9.0 with 10% HCl. After 20 days, no urea could be detected in the solution.[11] After 83 days, analysis indicated that the solution contained 4.00 mg (0.067 mmol, 1.2%) of urea based on starting cyanide.

C.—HCN (2 ml) was dissolved in about 300 ml of distilled water, and NH_4OH (*ca.* 3 *N*) was added to adjust the pH to 9.2. The solution was then made up to 500 ml in a volumetric flask using distilled water (*ca.* 0.15 *M* in HCN). The final pH was 9.3. A portion (*ca.* 20 ml) of this cloudy solution was placed in a glass bulb, degassed by four freeze–thaw cycles, and sealed under vacuum (0.3 Torr). The remainder of the solutions was left open to the atmosphere. Both solutions turned pale yellow after about 4 days. After 1 month, the nondegassed solution was found to be 0.135 *N* in cyanide.[15]

After 7 months, analysis of 1 ml of the nondegassed solution for urea[11] indicated that it contained 0.22 mg urea/ml (3.7×10^{-3} *M*) and that it was 0.024 *M* in cyanide ion.[15] Examination of the uv spectrum of this solution did not reveal any absorp-

tion at 296 nm due to diaminomaleonitrile (1 ml to 10 ml dilution). The presence of urea in this solution was confirmed by paper chromatography using BAW and Ehrlich's reagent.

The degassed solution was opened after 7 months and the pH was found to be 9.36. A uv spectrum (1 ml to 10 ml dilution) had a broad continuum from 200 to 450 nm. The absorption at 296 nm was 0.97 absorbance units but it was impossible from this to say whether diaminomaleonitrile was present. Analysis of the solution for diaminomaleonitrile by paper chromatography using BAW and Folin's reagent did not give a spot corresponding to authentic diaminomaleonitrile. This solution was 1.9×10^{-3} M in urea[11] and 0.053 M in cyanide.[15]

Portions (15 ml) of the degassed and nondegassed solutions were placed in round-bottom flasks and evaporated to dryness on the rotary evaporator. The two different samples (degassed and nondegassed) were worked up in the same way so as to compare them. The residue in each flask was taken up in 6 N hydrochloric acid and the solutions were sealed in vials and heated overnight at 110°. The solutions were concentrated to dryness, and the residues were taken up in 1 ml of water and analyzed for amino acids by paper chromatography using both BAW and PA and using ninhydrin for detection. Both solutions (degassed and nondegassed) gave spots corresponding to authentic glycine, which had also been spotted on the paper. Other ninhydrin-positive materials were also detected. The presence of urea in the degassed solution was confirmed by paper chromatography using BAW and Ehrlich's reagent.

Acknowledgment.—We thank Dr. W. A. Sheppard of E. I. du Pont de Nemours and Co. for a generous sample of diiminosuccinonitrile. This work was supported by Grant GP-19255 from the National Science Foundation, Grant NGR 30-018-148 from the National Aeronautics and Space Administration, and a Career Development Award (G. M. 6380) to J. P. F. from the U. S. Public Health Service.

Registry No.—**3**, 1187-42-4; **4**, 40982-16-9; **5**, 40982-17-0.

Pyridazines. LVIII. Oxidative Transformations of Pyridazinyl Sulfides

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Received March 21, 1973

Different oxidizing agents have been employed for conversion of methylthiopyridazines or their N-oxides into the corresponding methylsulfinyl or methylsulfonyl derivatives. In some cases, besides S-oxidation, N-oxidation also took place.

It is well known that organic sulfides can be transformed into sulfoxides or sulfones by a variety of oxidizing agents.[1] In the pyridazine series oxidation can, *a priori*, occur at either the sulfur containing side chain(s) or ring nitrogens to give the corresponding S-oxides or/and N_1- or N_2-oxides. The reported results on oxidation experiments with some pyridazinyl sulfides are either conflicting with regard to structure assignment or there has been no assignment at all. Pyridazinyl sulfides have been converted into the corresponding sulfones with potassium permanganate or hydrogen peroxide,[2-6] chlorine,[4,7] or sulfur dioxide.[4] For the synthesis of sulfoxides hydrogen peroxide[2,8] or m-chloroperoxybenzoic acid[9] was used, but, depending on the quantity of the oxidizing agent and reaction conditions, sometimes a mixture of the corresponding sulfoxides and sulfones resulted.[2,10] Pyridazinyl sulfoxides were transformed into sulfones with potassium permanganate.[11]

An extensive study of oxidative transformations of alkylthiopyridazines with various oxidizing agents was reported by Takahayashi,[12] but the obtained products were mostly designated as monoxides, dioxides, or trioxides. Moreover, he also assumed that in some cases, in addition to the formation of S-oxides, N-oxidation took place.[12,13] Moreover, halogens or alkoxy groups bound on the pyridazine ring can suffer hydrolysis and the corresponding pyridazinone derivatives were obtained.[14,15]

We have studied oxidations of pyridazinyl sulfides under differing conditions with different oxidizing agents. We used 70% hydrogen peroxide alone or in admixture with various solvents or in the presence of sodium tungstate, as well as dichloromonoperoxymaleic acid, bromine, potassium permanganate, chromium trioxide, potassium metaperiodate, and ceric ammonium nitrate.

The structures of some products were proved through chemical transformations. In addition, it is possible to distinguish between different oxidation products by nmr and/or ir spectra as well as on hand of color tests.[16-18] Thus, in an analogous series, when observing chemical shifts for a methylthio, methylsulfinyl, and methylsulfonyl group we observed a distinct deshielding effect of approximately 1 τ unit. This is comparable to that observed in 3- or 4-methylthiopyridazines and their oxidation products.[19,20] Infrared spectra are also of diagnostic value since one can

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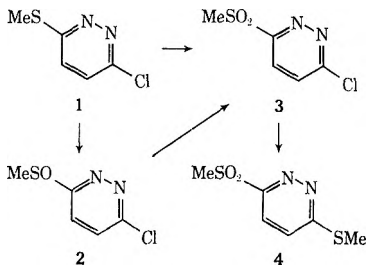
distinguish between a *N*-oxide and a sulfoxide group. The pyridazine *N*-oxides exhibit a N–O absorption in the 1333–1361-cm^{-1} region, in agreement with previous observations.[21,22] Similarly, all compounds assigned as pyridazine sulfoxides exhibit absorption in the 1042–1066-cm^{-1} region, also in accord with the known data.[23]

3-Chloro-6-methylthiopyridazine (**1**) when oxidized with an equivalent amount of hydrogen peroxide in glacial acetic acid afforded the corresponding sulfoxide (**2**) in good yield (see Scheme I). This compound was

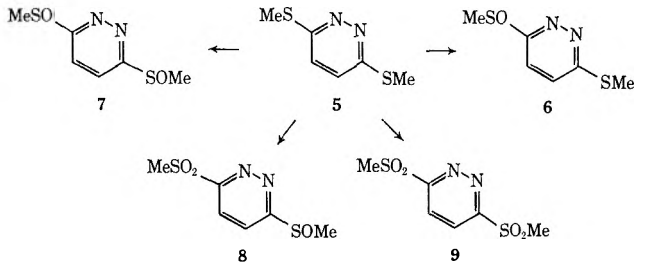
SCHEME I



previously prepared by oxidation with potassium permanganate and described as "monoxide."[12] With excess of peroxide the corresponding sulfone (**3**) was formed in a moderate yield. This compound is most probably identical with a dioxide, obtained by Takahayashi[12] from oxidation with potassium permanganate in acid solution. Furthermore, a second "monoxide" which was obtained by the same author from hydrogen peroxide oxidation in acetic acid was first assumed to be a *N*-oxide,[12] but was later identified[15] as 3-methylsulfonylpyridazin-6(1*H*)-one.

3,6-Bis(methylthio)pyridazine (**5**) could be selectively oxidized with hydrogen peroxide in acetic acid either into the monosulfoxide (**6**), disulfoxide (**7**), sulfoxide–sulfone (**8**), or disulfone (**9**) (Scheme II). The mono-

SCHEME II

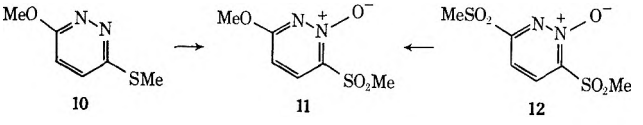


sulfone (**4**) could not be isolated from these experiments but was prepared from 3-chloro-6-methylsulfonylpyridazine and sodium methanethiolate. The monosulfoxide (**6**) could be obtained either from oxidation with bromine or with an equivalent amount of hydrogen peroxide in acetic acid. 3,6-Bis(methylsulfinyl)pyridazine (**7**) could be prepared from **5** by using only 82% of the required quantity of hydrogen peroxide. If dichloromonoperoxymaleic acid was used, a mixture of **7** and **8** was obtained from **5**. The disulfone (**9**) could be prepared either with dichloromonoperoxymaleic acid or with an excess of 70% hydrogen peroxide in glacial acetic acid or, in the optimum yield, in the presence of a catalytic amount of sodium tungstate. It should be mentioned that tungstate ions are known to be good catalysts for amine oxidations,[24] but also the corresponding sulfone could be obtained from 2-phenylmercaptoethanol in an improved yield in the presence of this catalyst.[25]

Application of other oxidizing agents was less effective since in most cases a mixture of products resulted. The progress of oxidation was followed by tlc. We could thus observe that after 30 min compound **5** was transformed with potassium permanganate in acetic acid at 50° into a mixture of **6**, **7**, **8**, and **9** with some of the starting material remaining unchanged. Oxidation with chromium trioxide in acetic acid at 65° and under controlled addition of the oxidizing agent, could lead to the formation of **6**. The reaction between **5** and potassium metaperiodate proceeded at room temperature very slowly. After 7 days the starting material was transformed completely into a mixture of **6** and **7**.

In all mentioned cases, no N-oxidation could be observed. However, the formation of a *N*-oxide took place when 3-methylthio-6-methoxypyridazine (**10**) was treated with an excess of hydrogen peroxide in trifluoroacetic acid with the formation of 3-methylsulfonyl-6-methoxypyridazine 2-oxide (**11**). On the other hand, the latter compound could also be obtained from 3,6-bis(methylsulfonyl)pyridazine 2-oxide (**12**) and sodium methylate (Scheme III).

SCHEME III



The two methylthio groups of 3,6-bis(methylthio)-pyridazine 1-oxide (**13**) displayed different reactivity. Application of the before-mentioned oxidizing agents revealed the preference for attack at the 3-methylthio group. In this manner, oxidation with bromine gave 3-methylsulfinyl-6-methylthiopyridazine 1-oxide (**14**). Partial oxidation with ceric ammonium nitrate followed with hydrogen peroxide gave the bis sulfoxide (**15**). On the other hand, oxidation with hydrogen peroxide in the presence of sodium tungstate afforded at room temperature a mixture of the bis sulfoxide (**15**) and sulfoxide–sulfone (**16**) in about equal quantity. Both compounds could be separated by tlc on silica. The same reaction, when conducted at 50° gave exclusively 3-methylsulfonyl-6-methylsulfinylpyridazine 1-oxide (**16**). The disulfone 1-oxide (**17**) could be obtained from **13** either with an excess of hydrogen peroxide in the presence of sodium tungstate or in acetic acid or, in moderate yield, with dichloromonoperoxymaleic acid (see Scheme IV).

From the above-described oxidation experiments we were not able to isolate 3-methylthio-6-methylsulfinylpyridazine 1-oxide (**18**). This compound could be obtained from **13** when using ceric ammonium nitrate

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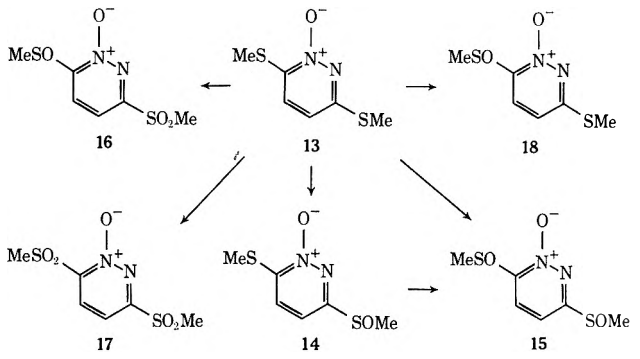
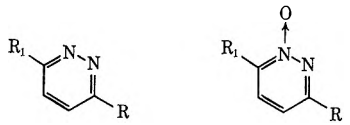
SCHEME IV



in aqueous acetonitrile as the oxidizing agent. Ceric ammonium nitrate, which was recently employed with success for conversion of diaryl sulfides into the corresponding sulfoxides[26] under mild conditions and without overoxidation, reacted in the above case regioselectively. This may be ascribed to the formation of a possible intermediate complex between the *N*-oxide function and the oxidizing agent, similarly as was observed with other substrates.[27]

As judged from experiments, where the progress of oxidation was followed by tlc, use of chromium trioxide in acetic acid is not recommended since a mixture of **14**, **15**, and **18** resulted from **13** at 65° after 1 hr.

Similar stepwise oxidation could be performed with 6-chloro-3-methylthiopyridazine 1-oxide (**20**, R = SMe, R_1 = Cl) and 3-methylthio-6-methoxypyridazine (**10**) to give the corresponding 3-methylsulfinyl (**20**, R = MeSO, R_1 = Cl, or **19**, R = SOMe, R_1 = OMe) or 3-methylsulfonyl analogs (**20**, R = $MeSO_2$,



R_1 = Cl, or **19**, R = SO_2Me, R_1 = OMe). In addition, the latter compound could be transformed into 6-methylsulfonyl-3-methoxypyridazine 1-oxide (**20**, R = OMe, R_1 = $MeSO_2$) with trifluoroperoxyacetic acid. Compound **20** (R = OMe, R_1 = $MeSO_2$) could be also obtained from the nucleophilic replacement of a methylsulfonyl group in 3,6-bis(methylsulfonyl)pyridazine 1-oxide (**17**) with sodium methylate. Other experiments of nucleophilic displacement proceeded similarly and showed that the 3-methylsulfonyl group is displaced preferentially. This parallels the reactivity of 3,6-dichloropyridazine 1-oxide with alkoxides[28] and other nucleophiles.[29,30]

Experimental Section

Melting points were taken on a Kofler micro hot stage. Nmr spectra were recorded on a JEOL JNM-C-60 HL spectrometer (TMS as internal standard) and mass spectra were taken on a Hitachi Perkin-Elmer RMU-6L instrument using direct sample insertion into the ion source. Throughout this paper 70% hydrogen peroxide was used.

The following compounds were prepared according to the procedures described in the literature: 3-Mercaptopyridazine-6(1*H*)-thione,[31] 3,6-bis(methylthio)pyridazine[32] [nmr (DMSO-d_6) τ 2.55 (s, H_4H_5), 7.40 (s, 3- and 6-SMe); nmr ($CDCl_3$) τ 2.92 (s, H_4H_5), 7.30 (s, 3- and 6-SMe)], and 3-chloro-6-methylthiopyridazine.[12]

3-Chloro-6-methylsulfinylpyridazine (**2**).—A warm solution of **1** (1.6 g) in glacial acetic acid (20 ml) was treated with hydrogen peroxide (0.5 g) and the mixture left at 50° for 2.5 hr. The solvent was evaporated *in vacuo*, the residue was treated with water and sodium bicarbonate and extracted with chloroform, and after evaporation of the solvent the product was purified by tlc (on silica, acetone, and ethyl acetate, 2:1 as the mobile phase and methanol for elution). The pure compound (1.6 g, 91%) had mp 74–79° (lit.[12] gives mp 73° for compound, described as "monoxide"); ir 1066 cm^{-1} (SO); nmr ($CDCl_3$) τ 1.68 and 2.08 (d, H_4 and H_5), 6.93 (s, SOMe), $J_{4,5}$ = 9.4 Hz.

Anal. Calcd for $C_5H_5ClN_2OS$: N, 15.86; S, 18.15. Found: N, 16.11; S, 18.30.

3-Chloro-6-methylsulfonylpyridazine (**3**).—A mixture of **1** (3.2 g), glacial acetic acid (40 ml), and hydrogen peroxide (4 g) was heated at 50° for 3 hr. The crystals which separated upon evaporation of the solvent *in vacuo* were washed with ethyl acetate and the product was crystallized from methanol (yield 1.3 g, 34%): mp 122–123° (lit.[12] gives mp 114° for a compound designated as "dioxide"); nmr ($CDCl_3$) τ 1.93 and 2.18 (d, H_4 and H_5), 6.55 (s, SO_2Me), $J_{4,5}$ = 9.5 Hz.

Anal. Calcd for $C_5H_5ClN_2O_2S$: N, 14.54; S, 16.65. Found: N, 14.48; S, 16.40.

3-Methylthio-6-methylsulfonylpyridazine (**4**).—A mixture of **3** (1.9 g), methanol (7 ml), and a solution of potassium methanethiolate (0.01 mol) in methanol was heated under reflux for 3 hr. Upon filtration the filtrate was evaporated to dryness and the product was crystallized from *n*-heptane and ethyl acetate (1:1) (yield 0.7 g, 34%): mp 92–95°: nmr ($CDCl_3$) τ 2.18 (d, H_5), 2.53 (d, H_4), 6.63 (s, SO_2Me), 7.25 (s, SMe), $J_{4,5}$ = 9.0 Hz.

Anal. Calcd for $C_6H_8N_2O_2S_2$: N, 13.72; S, 31.34. Found: N, 14.02; S, 31.10.

3-Methylthio-6-methylsulfinylpyridazine (**6**). **A.**—A warm solution of **5** (1.7 g) in glacial acetic acid (20 ml) was treated with hydrogen peroxide (0.5 g). After 2 hr at 40° the reaction mixture was evaporated *in vacuo;* the residue was neutralized with a solution of sodium bicarbonate and extracted with chloroform. The isolated product, obtained after evaporation of the solvent, was crystallized from ethyl acetate (yield 1.1 g, 59%): mp 118–119°; nmr ($CDCl_3$) τ 2.20 (s, H_5), 2.54 (s, H_4), 7.04 (s, 6-SOMe), 7.26 (s, 3-SMe), $J_{4,5}$ = 9.0 Hz; ir 1058 cm^{-1} (SO).

Anal. Calcd for $C_6H_8N_2OS_2$: N, 14.89; S, 34.11. Found: N, 14.70; S, 33.75.

B.—To a stirred solution of **5** (0.8 g) in dry chloroform (10 ml) a solution of bromine (0.8 g) in chloroform (1 ml) was added. Upon standing on ice, crystals of the bromine complex separated; they were filtered off and washed with *n*-hexane. The crystals were mixed with water and a solution of potassium hydroxide (0.6 g in a minimum amount of water) was added until a pH of 7 was attained. The mixture was extracted with chloroform, and upon evaporation of the solvent the product was found identical with the compound as prepared under A.

3,6-Bis(methylsulfinyl)pyridazine (**7**).—A mixture of **5** (3.5 g), glacial acetic acid (40 ml), and hydrogen peroxide (1.6 g) was heated on a water bath at 50° for 3 hr. Upon evaporation of the solvent *in vacuo*, the oily residue was treated with some water, neutralized with sodium bicarbonate, and extracted with chloroform. The product, obtained upon evaporation of the solvent (2.2 g 54%) was crystallized from methanol: mp 203–204°; ir 1053 cm^{-1} (SO); mass spectrum M^+ 204; nmr ($CDCl_3$) τ 1.58 (s, H_4, H_5), 6.97 (s, 3- and 6-SOMe).

Anal. Calcd for $C_6H_8N_2O_2S_2$: N, 13.72; S, 31.34. Found: N, 13.92; S, 31.40.

3-Methylsulfinyl-6-methylsulfonylpyridazine (**8**).—An ice-cold suspension of dichloromaleic anhydride (28 g) in dry methylene chloride (250 ml) was treated dropwise with hydrogen peroxide (4 g) and stirred 2 hr. Upon addition of **5** (5 g), the mixture was stirred for 1 hr. The separated product and dichloromaleic acid were filtered off, and after washing with water the residue was

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(30) T. Nakagome, *Yakugaku Zasshi*, **82**, 244 (1962); *Chem. Abstr.*, **58**, 3425 (1963).

(31) A. Pollak, B. Stanovnik, and M. Tišler, *Can. J. Chem.*, **44**, 829 (1966).

(32) J. Druey, K. Meier, and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).

neutralized with 10% sodium bicarbonate solution, filtered, and dried. The product was found identical with an authentic specimen of compound **9**. The methylene chloride layer was shaken with a 10% solution of sodium bicarbonate and dried and upon evaporation of the solvent the crude 3-methylsulfinyl-6-methylsulfonylpyridazine was crystallized from ethanol (0.7 g, 11%): mp 184–185°; mass spectrum M^+ 220; ir 1044 cm^{-1} (SO).

Anal. Calcd for $C_6H_8N_2O_3S_2$: N, 12.73; S, 29.07. Found: N, 12.81; S, 29.35.

3,6-Bis(methylsulfonyl)pyridazine (9). A.—A solution of dichloromonoperoxymaleic acid in methylene chloride was prepared exactly as described in the above case (**8**). After addition of **5** (1.7 g) the mixture was stirred for 1 hr. The separated product was filtered off and washed with water. The residue was crystallized from *N,N*-dimethylformamide (1.5 g, 64%): mp 278–279°; mass spectrum M^+ 236; nmr (DMSO-d_6) τ 1.35 (s, H_4 H_5), 6.48 (s, 3- and 6-$MeSO_2$).

Anal. Calcd for $C_6H_8N_2O_4S_2$: N, 11.86; S, 27.10. Found: N, 11.94; S, 27.20.

B.—A mixture of **5** (1.7 g), glacial acetic acid (20 ml), and hydrogen peroxide (2.5 g) was heated on water bath at 50°. After 30 min crystals of the disulfone started to separate. The product (1.5 g, 64%) was identical with the compound prepared as described under A.

C.—A mixture of **5** (3.4 g), a few crystals of sodium tungstate, water (40 ml), and hydrogen peroxide (6 g) was heated at 50° for 30 min. The separated product (4.2 g, 89%) was identical with the product obtained as described under A.

3-Methylthio-6-methoxypyridazine (10).—A mixture of **1** (6.5 g) and a solution of sodium methoxide in methanol (prepared from 1 g of sodium and 25 ml of methanol) was heated in an autoclave at 130° for 8 hr. The obtained product was crystallized from *n*-hexane (3.2 g, 50%): mp 88–89°; nmr (DMSO-d_6) τ 2.55 (d, H_4), 3.03 (d, H_5), 7.50 (s, SMe), 6.08 (s, OMe), $J_{4,5}$ = 9.2 Hz.

Anal. Calcd for $C_6H_8N_2OS$: N, 17.94; S, 20.49. Found: N, 17.96; S, 20.10.

3-Methylsulfinyl-6-methoxypyridazine (19, R = SOMe, R_1 = OMe).—The procedure was similar as for preparation of **2**. The product (0.8 g, 73%) was crystallized from *n*-hexane: mp 85–87°; nmr ($CDCl_3$) τ 2.10 (d, H_4), 2.94 (d, H_5), 7.10 (s, SOMe), 5.89 (s, OMe), $J_{4,5}$ = 9.0 Hz; ir 1042 cm^{-1} (SO).

Anal. Calcd for $C_6H_8N_2O_2S$: N, 16.27; S, 18.59. Found: N, 16.45; S, 18.30.

3-Methylsulfonyl-6-methoxypyridazine (19, R = $MeSO_2$, R_1 = OMe). A.—The same procedure as described for the preparation of **3** was followed. The product, obtained in 60% yield, had mp 99–102° (lit.[14] gives mp 99° for a "dioxide" with unspecified structure).

B.—A mixture of **9** (1.2 g) and sodium methoxide in methanol (prepared from 115 mg of sodium and 10 ml of methanol) was heated under reflux for 20 min. The product, obtained after evaporation of the solvent was crystallized from water (0.75 g, 79%), mp 99–102°. The product is identical in all respects with that obtained as described under A: nmr ($CDCl_3$) τ 2.08 (d, H_4), 2.92 (d, H_5), 6.66 (s, SO_2Me), 5.80 (s, OMe), $J_{4,5}$ = 9.0 Hz.

Anal. Calcd for $C_6H_8N_2O_3S$: N, 14.89; S, 17.01. Found: N, 15.34; S, 17.20.

3-Methoxy-6-methylsulfonylpyridazine 1-Oxide (11). A.—A mixture of 3-methoxy-6-methylthiopyridazine (156 mg), trifluoroacetic acid (3 ml), and hydrogen peroxide (0.5 g) was left at room temperature for 24 hr. The solvent was evaporated and the oily residue treated with water. The compound (0.1 g, 49%), mp 193–195°, is identical with the product obtained in B.

B.—A mixture of **12** (1.25 g) and methanolic sodium methoxide (prepared from 115 mg of sodium and 10 ml of methanol) was heated under reflux for 30 min. The separated product was filtered off and crystallized from ethanol (0.7 g, 69%): mp 193°; mass spectrum M^+ 204; nmr ($CDCl_3$) τ 1.75 (d, H_5), 3.20 (d, H_4), 5.86 (s, MeO), 6.53 (s, $MeSO_2$), $J_{4,5}$ = 9.0 Hz; ir 1333 cm^{-1} (N–O).

Anal. Calcd for $C_6H_8N_2O_4S$: N, 13.72; S, 15.67. Found: N, 13.96; S, 16.00.

3,6-Bis(methylthio)pyridazine 1-Oxide (13).—To an ice-cold solution of potassium methanethiolate in ethanol (prepared from 25 ml of methyl mercaptan, 27 g of potassium hydroxide, and 250 ml of ethanol) was added portionwise 3,6-dichloropyridazine 1-oxide[33] (35 g). Temperature was held below 60° and after addition was complete, the mixture was heated at 75° for 3 hr. The product was crystallized from ethanol (yield 34.5 g, 86%): mp 163°; nmr ($CDCl_3$) τ 2.76 (d, H_5), 3.09 (d, H_4), 7.43 (s, 3-SMe), 7.56 (s, 6-SMe), $J_{4,5}$ = 9.0 Hz; ir 1333 cm^{-1} (N–O).

Anal. Calcd for $C_6H_8N_2OS_2$: N, 14.89; S, 34.11. Found: N, 14.82; S, 34.10.

6-Methylthio-3-methylsulfinylpyridazine 1-Oxide (14).—To a stirred solution of **13** (0.9 g) in chloroform (10 ml) a solution of bromine (0.8 g) in chloroform (1 ml) was added dropwise. The separated bromine complex was filtered off and washed with *n*-hexane. It was then suspended in water and a solution of potassium hydroxide was added until pH 7. The mixture was extracted with chloroform and the isolated product was crystallized from a mixture of ethyl acetate and ethanol (yield 0.4 g, 41%): mp 148–151°; mass spectrum M^+ 204; nmr (DMSO-d_6) τ 2.42 (s, H_4), 1.96 (s, H_5), 7.11 (s, 6-SMe), 7.50 (s, 3-SOMe), $J_{4,5}$ = 8.5 Hz; ir 1340 cm^{-1} (N–O).

Anal. Calcd for $C_6H_8N_2O_2S_2$: N, 13.72; S, 31.34. Found: N, 13.92; S, 31.00.

3,6-Bis(methylsulfinyl)pyridazine 1-Oxide (15) and 3-Methylsulfonyl-6-methylsulfinylpyridazine 1-Oxide (16). A.—A stirred suspension of **13** (0.9 g) in acetone (10 ml) was treated with small amount of sodium tungstate in water, and hydrogen peroxide (0.5 g) was added dropwise. After 1 hr a clear solution was obtained and after 65 hr crystals of **16** separated. Upon filtration the filtrate was evaporated to dryness and the residue dissolved in chloroform. The filtered solution was evaporated and the product was purified by tlc (on silica, acetone as mobile phase and methanol for elution). The product, **15**, was crystallized from a mixture of toluene and *N,N*-dimethylformamide (yield 0.49 g, 46%): mp 201–202°; mass spectrum M^+ 220; nmr ($CDCl_3$) τ 1.54 (d, H_5), 2.00 (d, H_4), 7.01 (s, 6-SOMe), 6.96 (s, 3-SOMe), $J_{4,5}$ = 9.0 Hz; ir 1351 (N–O), 1058 cm^{-1} (SO).

Anal. Calcd for $C_6H_8N_2O_3S_2$: N, 12.73; S, 29.07. Found: N, 12.32; S, 29.10.

The sulfoxide–sulfone **16** was crystallized from toluene and *N,N*-dimethylformamide (yield 0.5 g, 44%): mp 193–195°; mass spectrum M^+ 236; ir 1053 (SO), 1359 cm^{-1} (N–O).

Anal. Calcd for $C_6H_8N_2O_4S_2$: N, 11.86; S, 27.10. Found: N, 12.01; S, 27.45.

B.—A solution of **13** (1.8 g) in aqueous acetonitrile (100 ml of 75%) was treated with ceric ammonium nitrate (11 g) and stirred until complete dissolution. The mixture was left at room temperature overnight, the solvent was evaporated, and the residue was extracted with chloroform. An analysis by tlc revealed that the product is a mixture of isomeric monosulfoxides. Therefore, the product (1.45 g) was dissolved in glacial acetic acid (10 ml), a small amount of sodium tungstate and hydrogen peroxide (0.35 g) was added. After 3 hr at 50°, the solvent was evaporated, the residue neutralized with sodium bicarbonate, and extracted with chloroform. Upon evaporation of the solvent the residue was crystallized from toluene and *N,N*-dimethylformamide. The compound was found to be identical in all respects with 3,6-bis(methylsulfinyl)pyridazine 1-oxide obtained as described under A.

C.—If a suspension of **13** (0.9 g) in water (10 ml) was treated with hydrogen peroxide (0.5 g) in the presence of a small quantity of sodium tungstate at 50°, the separated product was found to be **16** (0.25 g, 45%), identical with the product obtained as described under A.

3,6-Bis(methylsulfonyl)pyridazine 1-Oxide (17). A.—A mixture of **13** (0.9 g), water (10 ml), and hydrogen peroxide (1.5 g) was heated in the presence of a small amount of sodium tungstate at 50° for 1 hr. The separated product was crystallized from glacial acetic acid (yield 1.1 g, 92%): mp 262°; mass spectrum M^+ 252; nmr (DMSO-d_6) τ 1.28 (d, H_5), 1.98 (d, H_4), 6.45 (s, 3-SO_2Me), 6.55 (s, 6-SO_2Me), $J_{4,5}$ = 8.5 Hz.

Anal. Calcd for $C_6H_8N_2O_5S_2$: N, 11.11; S, 25.38. Found: N, 11.47; S, 25.40.

B.—Compound **13** (0.9 g) in glacial acetic acid (10 ml) was treated with hydrogen peroxide (2 g) at 50° for 3 hr. The product was found to be identical in all respects with that described under A (yield 0.9 g, 75%).

C.—Compound **13** (0.9 g) was treated with a solution of dichloromonoperoxymaleic acid (prepared from 8.0 g of dichloromaleic anhydride in 70 ml of methylene chloride and 3.0 g of hydrogen peroxide) for 1 hr. The product (0.75 g, 62%) was identical with that described under A.

3-Methylthio-6-methylsulfinylpyridazine 1-Oxide (18).—To a stirred solution of **13** (0.9 g) in aqueous acetonitrile (50 ml of 75%)

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ceric ammonium nitrate (5.5 g) was added and the mixture was left at room temperature overnight. The solvent was evaporated, the residue was extracted with chloroform, and upon evaporation of the solvent the product was crystallized from methanol (yield 0.85 g, 88%): mp 143–145°; nmr ($CDCl_3$) τ 2.19 (d, H_5), 2.86 (d, H_4), 7.00 (s, 6-SOMe), 7.40 (s, 3-SMe), $J_{4,5}$ = 8.5 Hz; ir 1049 (SO), 1332 cm^{-1} (N–O).

Anal. Calcd for $C_6H_8N_2O_2S_2$: N, 13.72; S, 31.34. Found: N, 13.65; S, 31.20.

6-Chloro-3-methylthiopyridazine 1-Oxide (20, R = SMe, R_1 = Cl).—To a stirred solution of 3,6-dichloropyridazine 1-oxide (33 g) in toluene (200 ml) at 70–85° was added dropwise an equivalent amount of potassium methanethiolate in methanol. After 5 hr the solvent was evaporated to dryness. The residue was treated with water and recrystallized from methanol (yield 10 g, 28%): mp 192–193°; mass spectrum M^+ 176; nmr ($CDCl_3$) τ 2.65 (d, H_5), 2.93 (d, H_4), 7.53 (s, SMe), $J_{4,5}$ = 9.0 Hz; ir 1340 cm^{-1} (N–O).

Anal. Calcd for $C_5H_5ClN_2OS$: N, 15.86; S, 18.15. Found: N, 15.74; S, 18.30.

6-Chloro-3-methylsulfinylpyridazine 1-Oxide (20, R = MeSO, R_1 = Cl).—A mixture of the above compound (0.9 g), glacial acetic acid (10 ml), hydrogen peroxide (0.25 g), and a small amount of sodium tungstate was left at room temperature. The separated crystals were crystallized from *n*-hexane and ethyl acetate (1:1) (yield 0.9 g, 92%): mp 131–132°; nmr ($CDCl_3$) τ 1.93 (d, H_5), 2.60 (d, H_4), 6.95 (s, SOMe), $J_{4,5}$ = 9.0 Hz; ir 1359 cm^{-1} (N–O), 1063 cm^{-1} (SO).

Anal. Calcd for $C_5H_5ClN_2O_2S$: N, 14.54; S, 16.64. Found: N, 14.44; S, 16.40.

6-Chloro-3-methylsulfonylpyridazine 1-Oxide (20, R = $MeSO_2$, R_1 = Cl).—The procedure was as described in the above case, except that the amount of hydrogen peroxide was greater (1.0 g) and reaction temperature 50° (1 hr). The product, obtained after evaporation of the solvent, was crystallized from *n*-hexane and ethyl acetate (1:1) (yield 0.6 g, 57%): mp 152°; mass spectrum M^+ 208; nmr ($CDCl_3$) τ 1.67 and 2.68 (d, H_4 and H_5), 6.55 (s, SO_2Me), $J_{4,5}$ = 9.0 Hz.

3-Hydrazino-6-methylsulfonylpyridazine (19, R = $NHNH_2$, R_1 = $MeSO_2$).—A suspension of 9 (1.2 g) in ethanol (7 ml) was treated with hydrazine hydrate (0.5 g of 100%), and the mixture was heated under reflux for 2 hr. Upon cooling on ice, the separated product was filtered and crystallized from ethanol (yield 0.85 g, 84%): mp 178–179°; nmr (DMSO-d_6) τ 2.87 (d, H_4), 2.22 (d, H_5), 6.73 (s, SO_2Me), 1.05 (broad, $NHNH_2$), 5.45 (broad, $NHNH_2$), $J_{4,5}$ = 9.0 Hz.

Anal. Calcd for $C_5H_8N_4O_2S$: N, 29.78; S, 17.01. Found: N, 29.75; S, 17.40.

6-Methylsulfonyl-3-piperidinopyridazine (19, R = $N(CH_2)_5$, R_1 = $MeSO_2$) was prepared in a similar way, except that *N,N*-dimethylformamide was used as solvent (at 60°). After addition of water the product separated and was crystallized from *n*-hexane and ethyl acetate (1:1) (yield 1.1 g, 90%): mp 124–125°; nmr ($CDCl_3$) τ 3.00 (d, H_4), 2.20 (d, H_5), 6.65 (s, SO_2Me), 6.20 and 8.25 (m, piperidine part), $J_{4,5}$ = 9.4 Hz.

Anal. Calcd for $C_{10}H_{15}N_3O_2S$: N, 17.42; S, 13.26. Found: N, 17.62; S, 13.26.

3-Hydrazino-6-methylsulfonylpyridazine 1-Oxide (20, R = $NHNH_2$, R_1 = $MeSO_2$).—The procedure was the same as in the case of the deoxygenated analog and 3,6-bis(methylsulfonyl)-pyridazine 1-oxide was used as starting material: mp 190–192° (from water, yield 83%); mass spectrum M^+ 204.

6-Methylsulfonyl-3-piperidinopyridazine 1-Oxide (20, R = $N(CH_2)_5$, R_1 = $MeSO_2$).—The compound was synthesized from 3,6-bis(methylsulfonyl)pyridazine 1-oxide in the same manner as described for the deoxygenated analog: mp 163–165° (from *n*-hexane and ethyl acetate (1:1), 71% yield); nmr (DMSO-d_6) τ 2.20 (d, H_5), 2.53 (d, H_4), 6.65 (s, 6-SO_2Me), 6.40, and 8.35 (m, piperidine part), $J_{4,5}$ = 9.2 Hz; ir 1361 cm^{-1} (N–O).

Anal. Calcd for $C_{10}H_{15}N_3O_3S$: N, 16.33; S, 12.44. Found: N, 16.61; S, 12.60.

Registry No.—**1**, 7145-61-1; **2**, 40953-86-4; **3**, 7145-62-2; **4**, 40953-88-6; **5**, 37813-54-0; **6**, 40953-90-0; **7**, 40953-91-1; **8**, 40953-92-2; **9**, 40953-93-3; **10**, 40953-94-4; **11**, 40953-95-5; **12**, 40953-96-6; **13**, 40953-97-7; **14**, 40953-98-8; **15**, 40953-99-9; **16**, 40954-00-5; **17**, 40953-96-6; **18**, 40954-02-7; **19** (R = SOMe, R, = OMe), 40954-03-8; **19** (R = $MeSO_2$, R_1 = OMe), 40954-04-9; **19** (R = $NHNH_2$, R_1 = $MeSO_2$), 40954-05-0; **19** (R = $N(CH_2)_5$, R_1 = $MeSO_2$), 40954-06-1; **20** (R = SMe, R_1 = Cl), 40954-07-2; **20** (R = MeSO, R_1 = Cl), 40954-08-3; **20** (R = $MeSO_2$, R_1 = Cl), 40954-09-4; **20** (R = $NHNH_2$, R_1 = $MeSO_2$), 40954-10-7; **20** [R = $N(CH_2)_5$, R_1 = $MeSO_2$], 40954-11-8; potassium methanethiolate, 26385-24-0; sodium methoxide, 124-41-4; 3,6-dichloropyridazine, 25974-26-9.

Photolysis and Spectral Properties of Some *N*-Sulfonyliminopyridinium Ylides

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Received April 26, 1973

The photolyses of the title compounds have been studied at different wavelengths and in different solvent systems. The main products are either the 1-sulfonyl-1,2-diazepine or the sulfonamide, depending on the reaction conditions. In no case was any evidence obtained for the formation of singlet sulfonyl nitrenes, although the sulfonamides may arise from triplet nitrene. The uv, nmr, and mass spectra of some of the compounds studied are reported and discussed briefly.

Sulfonyl nitrenes are almost always generated by the thermolysis of sulfonyl azides at 120° or higher.[1] In view of the observation that *N*-sulfonylazepines are the products of kinetic control of the reaction of singlet sulfonyl nitrenes with aromatic substrates while the *N*-phenylsulfonamides are the products of thermodynamic control,[2] it was desirable to develop a method of generating sulfonyl nitrenes at low (preferably ambient, or below) temperatures.

Of the various possible methods considered, photolysis of sulfonyl azides appeared the most obvious. Unfortunately, photolysis of aliphatic and aromatic sulfonyl azides in nonprotic, nonpolar solvents such as benzene or cyclohexane, or in a polar solvent such as pyridine, produces insoluble high-melting materials that have not been characterized.[3-5] When, however, the photolysis of methanesulfonyl azide was carried out in benzene at 25° such that the walls of the photolysis apparatus were not coated with tar, a very small amount of *N*-mesylazepine was isolated.[4] The only sulfonyl azide known to photolyze smoothly under these conditions is ferrocenylsulfonyl azide.[6] On the other hand, it has been reported that a number of nitrene derivatives can be produced by the photolysis of appro-

(1) R. A. Abramovitch and R. G. Sutherland, *Fortschr. Chem. Forsch.*, **16**, 1 (1970).

(2) R. A. Abramovitch and V. Uma, *Chem. Commun.*, 797 (1968).

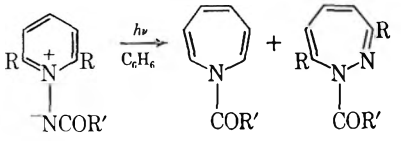
(3) L. Horner and A. Christmann, *Chem. Ber.*, **96**, 388 (1963).

(4) V. Uma, Ph.D. Thesis, University of Saskatchewan, 1967.

(5) W. Lwowski and E. Scheiffele, *J. Amer. Chem. Soc.*, **87**, 4359 (1965).

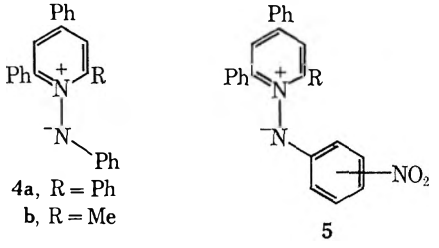
(6) R. A. Abramovitch, C. I. Azogu, and R. G. Sutherland, *Chem. Commun.*, 1439 (1969).

priate pyridinium *N*-ylides. Thus, photolysis of *N*-carbethoxyiminopyridinium ylides (**1**, R′ = OEt) in benzene gives a small amount of *N*-carbethoxyazepine (**2**) (and thence the phenylurethane), in addition to the *N*-carbethoxydiazepine (**3**, R′ = OEt) which is the main



1 **2**, R′ = OEt **3**

product.[7,8] The formation of **2** has been ascribed to the intervention of carbethoxynitrene. Photolysis of *N*-acetyliminopyridinium ylides (**1**, R′ = CH_3) in methylene chloride gave **3** (R′ = CH_3), the corresponding pyridine, and methyl isocyanate. The latter is the product of a photochemical Curtius rearrangement of, presumably, acetylnitrene.[9] Aryl nitrenes have also been postulated as being formed in the photolysis of suitable *N*-aryliminopyridinium ylides. It was concluded[10] that an excited singlet nitrene was formed in the photolysis of *N*,2,4,6-tetraphenyliminopyridinium ylide (**4a**) and of 2-methyl-*N*,4,6-triphenyliminopyridinium ylide (**4b**). On the other hand, photolysis of the



4a, R = Ph
b, R = Me

5

corresponding *N*-nitrophenyliminopyridinium ylides (**5**) gave results which suggested the formation of a nitrene intermediate, but not as an "excited" singlet.[11]

Photolysis of other *N*-imino ylides, in particular 4-imino-1,2,4-triazole derivatives,[12] have also been claimed to give nitrenes. The nature of the products generally indicates that, if a nitrene species is formed in this reaction, it is probably the triplet.

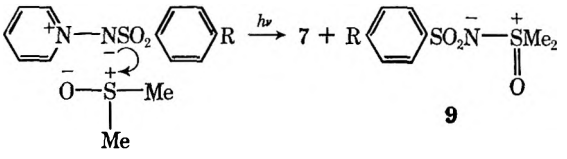
The photolysis of *N*-sulfonyliminopyridinium ylides under various conditions is now examined as a possible ambient-temperature source of singlet sulfonyl nitrenes in solution. The preparation of most of the ylides has already been described.[13] Others are reported in the Experimental Section. After this work was initiated two reports that the photolysis of *N*-sulfonyliminopyridinium ylides (**6**, R = C_6H_5,[14] *p*-$CH_3C_6H_4$[14,15]) gave the *N*-sulfonyldiazepine **7** appeared. Our work confirms this. Since our objective was the generation of sulfonyl nitrenes, we have examined this photolysis under a variety of conditions and find that the products formed vary markedly with the nature of the solvent. The results of photolyses of *N*-benzenesulfonyliminopyridinium ylide (**6**, R = C_6H_5) with 3000 Å radiation in various solvents are summarized in Table I.

TABLE I

PRODUCTS (% YIELD) FORMED IN THE PHOTOLYSIS (3000 Å) OF **6** (R = Ph) IN VARIOUS SOLVENTS

Solvent[a]	**7** (R = Ph)	$C_6H_5SO_2NH_2$ **8**	Recovered **6**	Other
C_6H_6–CH_3CN (10:1 v/v)	76	Trace	21	
C_6H_6–CH_3CN (1:1 v/v)	28	35	40	
Me_2SO	13		10	Sulfoximine **9** (R = Ph) (47%)
$C_6H_5NMe_2$	Trace	65		**10** (5%)
2,6-Lutidine	31	52	23	
C_6H_{12}–CH_2Cl_2 (2:1 v/v)	33	34	9	
Dioxane	28	61	35	**11** (trace)
Me_2CO	4	53		
C_6H_{10}–CH_2Cl_2 (2:1 v/v)	29	55	20	
MeOH	1.7	50	30	

[a] Degassed.



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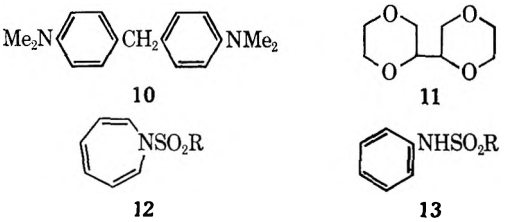
Initial photolyses were carried out in benzene in the expectation that, if singlet sulfonyl nitrenes were formed, they would be trapped either as the *N*-sulfonylazepines (**12**) or the *N*-sulfonylanilines (**13**).[2] Acetonitrile was added to give homogeneous solutions since the ylides are sparingly soluble in benzene and in cyclohexene and insoluble in cyclohexane. No **12** or **13** was ever detected,



10 **11**

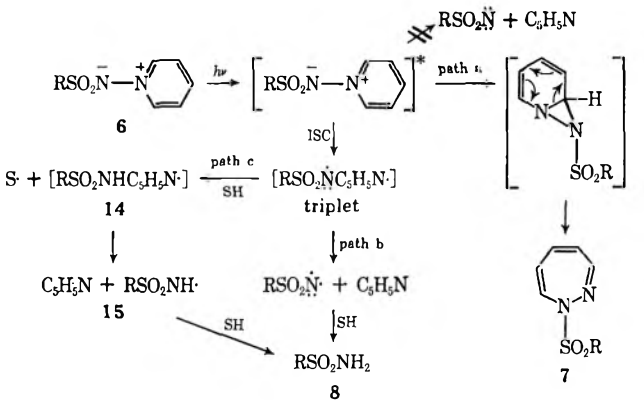
12 **13**

nor was any C–H insertion product[16] observed when the photolysis was carried out in cyclohexane. Neither was any insertion product or the aziridine[17] formed in the photolysis of a cyclohexene solution. When 2,6-lutidine was the solvent, no 3-sulfonylamido derivative[13] of this molecule was observed. Clearly, then, a singlet sulfonyl nitrene is *not* produced in these photolyses.

On the other hand, benzenesulfonamide (**8**, R = C_6H_5) was isolated in almost all the decompositions. This can be viewed as arising *via* path b (Scheme I) through a triplet sulfonyl nitrene which undergoes hydrogen abstraction. Alternatively, one can visualize hydrogen atom abstraction by the photoexcited pyri-

(7) J. Streith, A. Blind, J.-M. Cassal, and C. Sigwalt, *Bull. Soc. Chim. Fr.*, 948 (1969).
(8) T. Sasaki, K. Kanemaksu, A. Kakehi, I. Ichikawa, and K. Hayakawa, *J. Org. Chem.*, **35**, 426 (1970).
(9) V. Snieckus, *Chem. Commun.*, 831 (1969).
(10) V. Snieckus and G. Kan, *Chem. Commun.*, 172 (1970).
(11) C. W. Bird, I. Partridge, and D. Y. Wong, *J. Chem. Soc., Perkin Trans. 1*, 1020 (1972).
(12) H. G. O. Becker, *J. Prakt. Chem.*, **312**, 1112 (1971); *Z. Chem.*, **10**, 264 (1970); G. V. Boyd and A. J. H. Summers *J. Chem. Soc. B*, 1648 (1971).
(13) R. A. Abramovitch and T. Takaya, *J. Org. Chem.*, **37**, 2022 (1972).
(14) J. Streith and J.-M. Cassal, *Tetrahedron Lett.*, 4541 (1968).
(15) A. Balasubramanian, J. M. McIntosh, and V. Snieckus, *J. Org. Chem.*, **35**, 433 (1970).
(16) M. F. Sloan, D. S. Breslow, and W. B. Renfrow, *Tetrahedron Lett.*, 2905 (1964).
(17) R. A. Abramovitch, C. I. Azogu, and R. G. Sutherland, *Tetrahedron Lett.*, 1637 (1971).

SCHEME I



dinium ylide taking place to give **14** which would undergo N–N bond cleavage to yield $RSO_2NH\cdot$ (**15**) and pyridine, followed by further hydrogen abstraction by **15** to give the sulfonamide observed (path c, Scheme I). It is not possible at this time to decide between the alternatives. There is some precedent for the formation of excited radical species on photoexcitation; thus irradiation of amines in the presence of aromatic hydrocarbons gives excited charge-transfer complexes (in nonpolar solvents) or radical ions (in aprotic solvents).[18] It has been suggested[8] that the formation of diazepine **3** (R′ = OEt) proceeds *via* an excited triplet state because the yields of **3** obtained were better when **1** (R′ = OEt) was irradiated in acetone (a triplet sensitizer) solution than when it was dissolved in benzene or in dioxane. In contrast to this, photolysis of **6** (R = Ph) in acetone gave only a 4% yield of diazepine **7** (R = Ph) and a 53% yield of hydrogen-abstraction product. Photolysis in benzene, however, gave a high yield of the diazepine and only a trace of the sulfonamide. These results confirm that **8** is a product of a triplet intermediate and suggests that *N*-sulfonyldiazepine arises from a singlet excited state. When dioxane was the solvent, a trace of dioxanyldioxane (**11**) was observed in addition to **7** and **8**, and probably arises by hydrogen abstraction followed by radical coupling. Photolysis of **6** (R = Ph) in *N*,*N*-dimethylaniline (a good electron donor solvent) gave only traces of diazepine: the main product was the sulfonamide, but some 4,4′-methylenebis(*N*,*N*-dimethylaniline) (**10**) was also formed. It is of interest the **10** was also formed in other nitrene reactions: thermolysis of sulfonyl azides[19] and of *p*-nitrophenyl azide[20] in *N*,*N*-dimethylaniline. It was suggested[20] that a formaldehyde precursor, *e.g.*, $PhN(Me)CH_2\cdot$, was the active condensing agent, and this would be in agreement with the present contention that a triplet diradical intermediate is formed in this photolysis.

In view of the above, it seems unlikely that the sulfoximine **9** (R = H) formed from **6** on irradiation in DMSO results from a *free* singlet sulfonyl nitrene being trapped by the solvent. Thermolysis of **6** (R = Ph or *p*-$CH_3C_6H_4$) in DMSO at 100–110° in the presence of copper powder gave only unchanged **6**. Photolysis (2537 Å) of **6** (R = *p*-$CH_3C_6H_4$) in DMSO gave **9** (R = CH_3) (34%) together with **7** (R = *p*-$CH_3C_6H_4$) (12%). We propose that a complex is formed between the singlet excited ylide and this solvent and that **9** is formed concertedly with the elimination of pyridine.

The influence of wavelength on the relative yields of products was examined briefly in the photolysis of **6** (R = *p*-$CH_3C_6H_4$) (λ_{max} 237, 313 mμ) in benzene–acetonitrile (10:1 v/v) solution. The results are given in Table II.

TABLE II

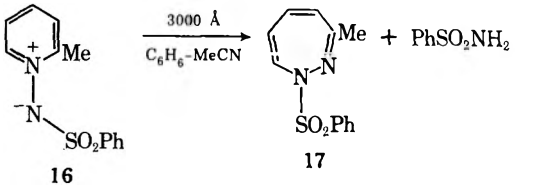
INFLUENCE OF WAVELENGTH ON THE YIELDS OF PRODUCTS FORMED ON PHOTOLYSIS OF **6** (R = *p*-$CH_3C_6H_4$) IN C_6H_6–CH_3CN (10:1 v/v)

	Yield, %		
Main wavelength, Å[a]	**7** (R = *p*-$CH_3C_6H_4$)	*p*-$CH_3C_6H_4SO_2NH_2$ (**8**)	Recovered **6**
2537[b]	14	12	32
3000[c]	74	Trace	24
3500[c]	16	17	47

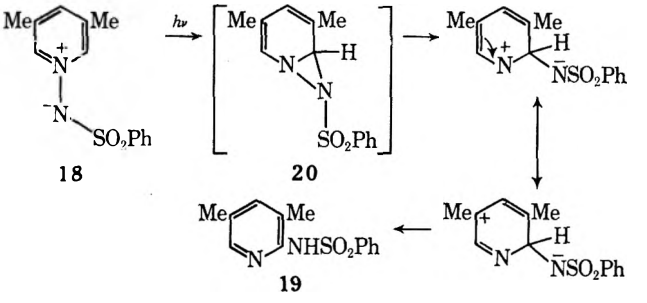
[a] A Rayonet photochemical reactor (RPR-100) was used with RPR-2537 Å (*ca.* 35 W), RPR-3000 Å (*ca.* 21 W), and RPR-3500 Å lamps, respectively. [b] Quartz flask. [c] Pyrex filter.

As can be seen, the best yields of **7** were obtained using 3000 Å lamps but low yields were achieved with the others. On the other hand, high yields of **3** (R′ = OEt) have been reported for the photolysis of **1** (R′ = OEt) in methylene chloride solution at 3500 Å.[15] It is also interesting to note that **7** and **8** are formed in almost equal amounts when 2537 or 3500 Å lamps are used, but only trace amounts of the hydrogen-abstraction product are formed at 3000 Å.

The effect of alkyl groups in the pyridine ring was also briefly studied. Photolysis (3000 Å) of *N*-benzenesulfonylimino-2-methylpyridinium ylide (**16**) in benzene–acetonitrile (10:1 v/v) again gave mainly (54%) 1-benzenesulfonyl-3-methyldiazepine (**17**) to-



gether with a small amount (5%) of benzenesulfonamide. The orientation of the methyl group in **17** was established by its nmr spectrum and is the same as that in the *N*-carbethoxydiazepine obtained from the corresponding 2-picolinium ylide.[15] Thus, cyclization again takes place preferentially to the unsubstituted α position. On the other hand, irradiation of *N*-benzenesulfonylimino-3,5-dimethylpyridinium ylide (**18**) at 3000 Å in C_6H_6–CH_2Cl_2 (10:1 v/v) gave 2-benzenesulfonamido-



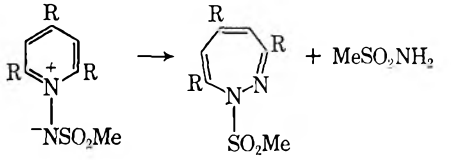
(18) C. Pac and H. Sakurai, *Tetrahedron Lett.*, 3829 (1969); N. Mataga and K. Ezumi, *Bull. Chem. Soc. Jap.*, **40**, 1355 (1967); R. S. Davidson, *Chem. Commun.*, 1450 (1969).

(19) T. Curtius and J. Rissom, *J. Prakt. Chem.*, **125**, 311 (1930).

(20) R. A. Abramovitch and E. F. V. Scriven, *Chem. Commun.*, 787 (1970); R. A. Abramovitch, S. R. Challand, and E. F. V. Scriven, *J. Org. Chem.*, **37**, 2705 (1972).

3,5-dimethylpyridine (**19**) (18%) and benzenesulfonamide (33%). 2-Carbethoxyamino-3,5-dimethylpyridine has been obtained similarly from 3,5-dimethyl-1-carbethoxyiminopyridinium ylide.[15] These probably arise by ring opening of the intermediate pyridodiaziridine (**20**), opening to the otherwise unfavorable dipolar species being facilitated by delocalization of the positive charge over the methyl-bearing carbon atoms.

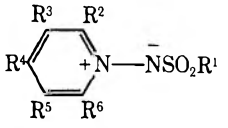
No evidence for the generation of singlet sulfonyl nitrenes could be obtained from the photolysis of *N*-methanesulfonyliminopyridinium ylides (**21**, R = H or CH_3). Again, the only products formed were the diazepines (**22**) and methanesulfonamide. Compound



21 (R = CH_3) was sufficiently soluble in benzene that its irradiation in that solvent alone could be studied. This did not give rise to any new products (other than tars).

Uv, Nmr, and Mass Spectra.—In the course of this work the spectroscopic properties of the ylides and diazepines have been determined. We have already reported[13] the infrared and nmr spectra of the ylides. Table III gives the uv characteristics of ylides studied here and earlier.

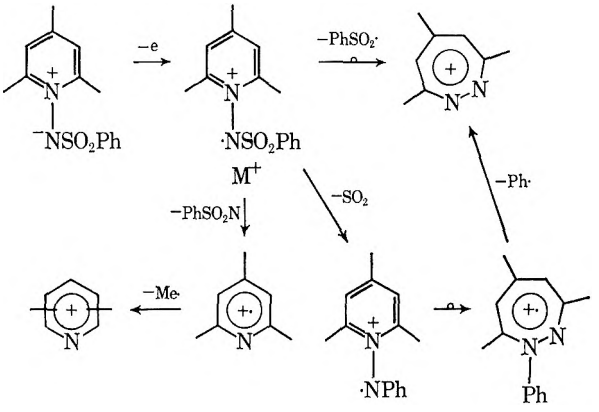
TABLE III
UV SPECTRA OF YLIDES IN EtOH



Compd[a]	Registry no.	λ_{max}, mμ[b]	ε × 10⁻³
R^1 = Ph	28460-28-8	244	11.6
		312	2.0
R^1 = Ph; R^2 = Me	34456-58-1	244	10.7
		311	1.5
R^1 = Ph; R^2 = R^4 = R^6 = Me	34456-63-8	246	12.8
		(295)	1.1
R^1 = Ph; R^4 = CN	34456-64-9	273	8.6
		350	7.7
R^1 = Ph; R^3 = R^5 = Me	34456-61-6	243	13.6
		310	2.4
R^1 = *p*-$CH_3C_6H_4$	40949-56-2	237	13.0
		313	2.1
R^1 = Me	34456-51-4	245	8.3
		308	2.0
R^1 = R^2 = R^4 = R^6 = Me	40949-58-4	245	9.3
		271	4.8
		(295)	0.9
R^1 = *o*-biphenylyl[c]	40949-59-5	238	13.8
		307	3.0
R^1 = *o*-biphenylyl; R^2 = R^4 = R^6 = Me[c]	40949-60-8	241	16.8
		(297)	1.0
R^1 = Ph; R^2,R^3 = R^4,R^5 = —CH=CH—CH=CH—[c]	40949-61-9	255	95.6
		324	1.9
		339	4.2
		356	7.2
		378	4.7

[a] Substituents R" are H unless otherwise indicated. [b] Figures in parentheses indicate points of inflection. [c] The preparation and properties of these ylides will be reported in a forthcoming paper.

The mass spectra of the ylides all exhibit parent ions, as can be seen from Table IV. When 2 substituents are present, the M^+ peak is of lower intensity than otherwise. These then fragment to give either the diazepinium ion with loss of $PhSO_2$, or N–N bond cleavage occurs to give the pyridinium cations. Since fragments arising from the loss of methyl from the diazepinium ions are of relatively low intensity, it appears as though nuclear methyl groups are lost mainly from the substituted pyridinium radical cation. Loss of SO_2 from the parent ion is also a prominent fragmentation pathway.



A glance at the uv absorption maxima given in Table III clearly suggests that the less intense higher wavelength absorption of the two usually observed for these ylides is associated with a transition of the lone pair of electrons on the imino nitrogen atom. When 2,6 substituents are present in the pyridine ring which would force the RSO_2 group out of coplanarity with that ring, this band moves to higher frequencies, while the lower wavelength band (π,π^*) is relatively unaffected.

The nmr spectral assignments for the diazepines are very similar to those made[15] for the corresponding *N*-carbethoxy derivatives and for the known sulfonyl derivatives.

Experimental Section

Nmr spectra were determined on a Varian HA-100 spectrometer and mass spectra on a CEC 21-104 single focusing instrument at 70 eV.

1-Methanesulfonylimino-2,4,6-trimethylpyridinium Ylide.—A solution of methanesulfonyl hydrazide (5.50 g) and 2,4,6-trimethylpyrilium perchlorate (11.1 g) in methanol (200 ml) was boiled under reflux for 18 hr on a steam bath. The solution was concentrated to 50 ml *in vacuo*, and a solution of KOH (5.5 g) in H_2O (10 ml) was added portionwise with cooling. The mixture was stirred for 1 hr at room temperature, the potassium chlorate which separated was filtered, and the filtrate concentrated and chromatographed on basic alumina. Elution with CH_2Cl_2 gave the desired ylide (8.5 g, 80%): mp 149.5–150.5° (from benzene); mass spectrum *m/e* (rel intensity) 214 (23, M^+), 135 (100, $M^+ - CH_3SO_2\cdot$), 121(19, $M^+ - CH_3SO_2N$).

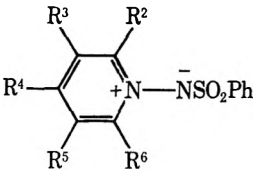
Anal. Calcd for $C_9H_{14}N_2O_2S$: C, 50.45; H, 6.59. Found: C, 50.59; H, 6.55.

Photolysis of 6 (R = Ph) in Benzene–Acetonitrile.—The general procedure used in the photolyses is similar to that illustrated below.

A.—A solution of ylide **6** (R = Ph) (1.17 g) in a mixture of benzene (600 ml) and acetonitrile (60 ml) was irradiated in a Pyrex flask under dry N_2 at room temperature for 24 hr using Rayonet RPR-3000 Å lamps. The yellow solution was evaporated under vacuum to give a brown residue which was chromatographed on a column of silica gel (35 g). Elution with ether–petroleum ether (bp 30–60°) (4:1 v/v) gave 1-benzenesul-

TABLE IV

MASS SPECTRAL DATA FOR *N*-BENZENESULFONYLIMINOPYRIDINIUM YLIDES,[a] *m/e* (RELATIVE INTENSITY)[b,c]



	6	R² = Me (34456-58-1)	R⁴ = Me (34456-59-2)	R³ = Me (34456-60-5)	R³ = R⁵ = Me (34456-61-6)	R² = R⁶ = Me (34456-62-1)	R² = R⁴ = R⁶ = Me (34456-63-8)	R⁴ = CN (34456-64-9)
M^+	234 (35)	248 (8)	248 (60)	248 (75)	262 (21)	262 (6)	276 (5)	259 (28)
			247 (21)					
$M^+ - SO_2$	170 (100)	184 (17)	184 (46)	184 (60)	198 (21)	198 (23)	212 (44)	195 (10)
	169 (32)	168 (18)	183 (21)	183 (33)			197 (13)	157 (14)
	157 (15)						196 (18)	
	141 (26)							141 (13)
$M^+ - C_6H_5SO_2\cdot$	93 (16)	107 (100)	107 (54)	107 (56)	121 (30)	121 (100)	135 (100)	118 (26)
			94 (30)					
$M^+ - C_6H_5SO_2N$	79 (15)	93 (26)	93 (83)	93 (100)	107 (100)	107 (22)	121 (28)	104 (67)
					106 (47)	106 (11)	106 (84)	
					94 (25)	94 (19)		
						93 (12)		93 (14)
		92 (14)			92 (21)	92 (67)		
				91 (44)	91 (38)	91 (18)	91 (38)	91 (54)
		79 (39)	80 (30)	80 (53)	79 (45)		79 (35)	
			78 (62)	78 (67)	78 (77)	78 (12)		78 (15)
Ph^+	77 (23)	77 (99)	77 (100)	77 (90)	77 (87)	77 (27)	77 (49)	77 (100)
							67 (15)	76 (13)
		76 (52)	66 (29)	66 (28)	65 (22)	65 (19)	65 (20)	64 (31)
		53 (26)	53 (46)	53 (50)	53 (31)	53 (17)		63 (19)
	52 (11)	52 (19)			52 (24)			
	51 (18)	51 (51)	51 (70)	51 (70)	51 (60)	52 (21)	51 (34)	51 (37)
					50 (24)			50 (28)
	44 (20)				41 (26)	41 (11)	41 (39)	41 (11)
$C_3H_3^+$	39 (12)	39 (30)	39 (40)	39 (60)	39 (52)	39 (21)	39 (34)	39 (22)

[a] Substituent H unless otherwise specified. [b] Only fragment ions with more than 10% relative intensities are reported. [c] Registry numbers found in table headings.

fonyl-(1*H*)-1,2-diazepine (7, R = Ph) (76%): mp 147–148°; identical (ir, nmr) with the product described in the literature;[14,15] mass spectrum *m/e* (rel intensity) 234 (11, M^+), 170 (11, $M^+ - SO_2$), 93 (33, $M^+ - PhSO_2\cdot$) (no peak at *m/e* 79 corresponding to the loss of $PhSO_2N$).

Anal. Calcd for $C_{11}H_{10}N_2O_2S$: C, 56.40, H, 4.30. Found: C, 56.31; H, 4.52.

Elution with ether gave diazepine contaminated with traces of benzenesulfonamide (mp 138–144°). The sulfonamide could be resolved from the azepine by thin layer chromatography on silica gel using chloroform–methanol (10:1 v/v) as the developer. Elution with ether–methanol (3:1 v/v) gave unreacted ylide (260 mg, 21%).

B.—When the photolysis was repeated using a 1:1 mixture of benzene and acetonitrile (total volume 660 ml), chromatography as before gave diazepine (28%), benzenesulfonamide (35%), mp 151–153°, undepressed on admixture with an authentic sample, and starting ylide (40%).

Photolysis of 6 (R = Ph) in DMSO.—From 6 (R = Ph) (0.468 g) in DMSO (300 ml) were obtained diazepine 7 (R = Ph) (13%), dimethyl sulfone (53 mg), mp 109–110°, identical with an authentic sample, and *N*-benzenesulfonyldimethylsulfoximine (9, R = Ph) (0.219 g, 47%), mp 115–116° (lit.[21] 115°), identical with an authentic sample. Starting material (46 mg) was also recovered.

Photolysis of 6 (R = Ph) in Dioxane.—In addition to the diazepine (28%), mp 146–147°, and benzenesulfonamide (61%), mp 152–154°, there was obtained from 6 (R = Ph) (1.17 g) a crude colorless product (30 mg) which, on tlc, indicated the presence of two components. Fractional crystallization from methanol–ether gave *meso*-dioxanyldioxane (4 mg), mp 156–158° (lit.[22] 157°), mass spectrum *m/e* 174 (M^+). The other component may be the *dl* isomer (lit.[22] mp 131°), but insufficient pure material could be obtained for identification. Starting ylide (35%) was recovered.

Photolysis of 6 (R = Ph) in *N,N*-dimethylaniline gave only benzenesulfonamide (65%), mp 152–154°, and 4,4′-methylenebis(*N,N*-dimethylaniline) (5%), mp 90° (lit.[23] mp 90°).

Photolysis of 1-Methanesulfonyliminopyridinium Ylide (21, R = H).—A suspension of 1-methanesulfonyliminopyridinium ylide (1.03 g) in a mixture of benzene (600 ml) and acetonitrile (100 ml) was irradiated using the RPR-3000 Å lamps for 40 hr. Chromatography of the reaction products on basic alumina gave 1-methanesulfonyl-(1*H*)-1,2-diazepine (22, R = H) (75 mg, 7%): mp 110–111° (from ether–light petroleum ether); ir (KBr) (main peaks only) 1625 (w), 1610 (m), 1353 (vs) 1316 (s), 1170 (vs), 961 (m), 787 (m), 765 (s),730 cm^{-1} (s); nmr $\tau_{TMS}^{CDCl_3}$ 7.07 (s, 3 H, $-SO_2CH_3$), 4.28 (dq, $J_{6,7}$ = 7.5 Hz, $J_{5,6}$ = 5.0 Hz, $J_{4,6}$ = 1.0 Hz, 1 H, C_6-H), 4.01 (d, $J_{6,7}$ = 7.5 Hz, 1 H, C_7-H), 3.71 (dd, $J_{4,5}$ = 11.0 Hz, $J_{3,4}$ = 3.5 Hz, $J_{4,6}$ = 1.0 Hz, 1 H, C_4-H), 3.47 (q, $J_{4,5}$ = 11.0 Hz, $J_{5,6}$ = 5.0 Hz, 1 H, C_5-H), 2.72 (d, $J_{3,4}$ = 3.5 Hz, 1 H, C_3-H); mass spectrum *m/e* (rel intensity) 172 (9, M^+), 93 (70, $M^+ - CH_3SO_2\cdot$), 66 (35), 39 (100, $C_3H_3^+$).

Anal. Calcd for $C_6H_8N_2O_2S$: C, 41.85; H, 4.68. Found: C, 42.05, H, 4.68.

Elution with chloroform gave methanesulfonamide (68 mg, 12%), mp 89–91°, identical with an authentic sample. Elution with $CHCl_3$–MeOH gave starting ylide (0.55 g, 55%).

Photolysis of 21 (R = CH_3).—A solution of the ylide (1.07 g) in benzene (600 mg) was irradiated as above for 80 hr. Chromatography of the products yielded the diazepine (22, R = Me) (0.35 g, 35%): mp 126.5–127° (from ether–petroleum ether); ir (KBr) (main peaks only) 1642 (s), 1610 (s), 1577 (s), 1378 (s), 1330 (vs), 1200 (s), 1163 (vs), 1065 (s), 990 (s), 970 (s), 845 (s), 780 (s), 735 cm^{-1} (s); nmr $\tau_{TMS}^{CDCl_3}$ 8.11 (s, 3 H, C_5-CH_3)

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7.94 (s, 3 H, C_7-CH_3), 7.80 (s, H, C_3-CH_3), 6.91 (s, 3 H, SO_2-CH_3), 4.28 (br s, 1 H, C_6-H), 3.83 (br s, 1 H), C_4-H); mass spectrum *m/e* (rel intensity) 214 (19, M^+), 135 (100, $M^+ - CH_3SO_2\cdot$), 121 (19, $M^+ - CH_3SO_2N$), 106 (25), 39 (12).

Anal. Calcd for $C_9H_{14}N_2O_2S$: C, 50.45; H, 6.59. Found: C, 50.60; H, 6.59.

Elution with methylene chloride gave methanesulfonamide (60 mg, 12.5%). Elution with chloroform–methanol gave starting ylide (172 mg, 16%).

Photolysis of 1-Benzenesulfonylimino-2-methylpyridinium Ylide (16).—This was carried out in benzene–acetonitrile (6:1 v/v) to give the diazepine **17** (54.1%): mp 118.5–119°; nmr $\tau_{TMS}^{CDCl_3}$ 8.00 (s, 3 H, C_3-CH_3), 4.36 (dq, $J_{6,7}$ = 7.0 Hz, $J_{5,6}$ = $J_{6,7}$ = 3.5 Hz, $J_{4,6}$ = 0.5 Hz, 1 H, C_6-H), 4.04 (dd, $J_{6,7}$ = 7.0 Hz, $J_{5,7}$ = 0.5 Hz, 1 H, C_7-H), 3.58 (d, $J_{5,6}$ = $J_{4,5}$ = 3.5 Hz, 2 H, C_4-H and C_5-H), 2.50 (m, $J_{\alpha,\beta}$ = $J_{\alpha',\beta'}$ = 8 Hz, 3 H, C_β-H, $C_{\beta'}$-H, C_α-H), 2.04 (dd, $J_{\alpha,\beta}$ = $J_{\alpha',\beta'}$ = 8.0 Hz, $J_{\alpha,\gamma}$ = $J_{\alpha',\gamma}$ = 2.0 Hz, 2 H, C_α-H, $C_{\alpha'}$-H); mass spectrum *m/e* (rel intensity) 248 (7, M^+), 107 (100, $M^+ - PhSO_2\cdot$), 93 (21, $M^+ - PhSO_2N$), 77 (70, Ph^+), 39 (37).

Anal. Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87. Found: C, 58.33; H, 5.08.

Benzenesulfonamide (5.2%), mp 153–155°, and starting ylide (31%) were also isolated.

Photolysis of 1-Benzenesulfonylimino-3,5-dimethylpyridinium Ylide (18).—This photolysis was effected on a benzene–methylene chloride (10:1 v/v) solution using RPR-3000 Å lamps for 80 hr. Chromatography on basic alumina gave a yellow solid (<1%), mp 118–119°, which could be the diazepine but was not available in sufficient quantity for characterization and 2-benzenesulfonylamino-3,5-dimethylpyridine (**19**) (18%), mp 132° (from benzene–cyclohexane), identical with a sample synthesized from 2-amino-3,5-dimethylpyridine and benzenesulfonyl chloride in pyridine: ir (KBr) (main bands only) 3250 (s), 1600 (vs), 1540 (s), 1408 (s), 1372 (s), 1340 (s), 1245 (s), 1130 (s), 1080 (vs), 983 (s), 936 (s), 740 (s), 720 (s), 695 cm^{-1} (s); mass spectrum *m/e* (rel intensity) 262 (4, M^+), 197 (100, $M^+ - H\cdot - SO_2$), 121 (41, $M^+ - PhSO_2\cdot$), 77 (46), 39 (20).

Anal. Calcd for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38. Found: C, 59.67; H, 5.53.

Benzenesulfonamide (33%) and starting ylide (8.5%), mp 209–211°, were also isolated.

Acknowledgments.—The authors are indebted to the National Science Foundation (NSF-GP-18557) for the support of this work. We are also grateful to the Reilly Tar and Chemical Corporation for the gift of the starting pyridines used here.

Registry No.—**7** (R = Ph), 20169-41-9; **17**, 40988-50-9; **19**, 40949-66-4; **22** (R = H), 40949-67-5; **22** (R = Me), 40949-68-6; methanesulfonyl hydrazide, 10393-86-9; 2,4,6-trimethylpyridium perchlorate, 940-93-2.

Reactivity of Thiazole in Electrophilic Reactions as Determined from Solvolysis Rates[1]

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Received April 3, 1973

Solvolysis rates for the three isomeric 1-thiazolylethyl chlorides have been determined in 80% ethanol. The general reactivity of thiazole in electrophilic substitution reactions has been discussed and the decreasing order of reactivity of 5-thiazolyl > 4-thiazolyl > phenyl > 2-thiazolyl has been established.

The solvolysis of α-arylethanol derivatives is a useful probe of aromatic reactivity. Streitwieser, *et al.*,[2-4] have recently compared the reactivities of a large number of aromatic hydrocarbons, and the solvolysis rates of the corresponding arylmethyl tosylates. There is good correspondence in the two series, covering a wide variety of types and conditions,[2] and to various semiempirical MO methods;[4] the results lead to a useful set of σ constants for the aromatic moiety, designated σ^+ by Streitwieser.[3]

This concept has been extended to heterocyclic systems by Hill,[5] by the senior author,[6] by Taylor,[7] and by Marino.[8] Particularly pertinent are the observed relationships of reactivity of thiophene and its derivatives[6,9] and of furan and its derivatives.[10]

The solvolysis reaction has several distinct advantages for the investigation of basic heterocyclic systems, as it avoids the uncertainties of whether reaction is occurring *via* the protonated form or the free base. Studies from these laboratories have established σ^+ values for pyridine moieties in this fashion.[11]

In the present study we examine the thiazole system. Each of the isomeric 1-(thiazolyl)ethyl chlorides was prepared and solvolyzed. The data are given in Table I, and the rates are compared to the solvolysis rate for 1-phenylethyl chloride, which is of similar reactivity. (See Table I.)

From the rate data in Table I, we calculate σ^+ values appropriate for the various thiazole moieties,[12] using ρ for the solvolysis −5.12.[13] Thus the replacement σ_{Ar}^+ are as follows: 5-thiazolyl −0.18; 4-thiazolyl −0.01; 2-thiazolyl +0.26.

There have been a number of MO calculations carried out on thiazole. Metzger and his coworkers[14] have recently summarized calculations carried out to various levels of sophistication. All of these methods agree that the reactivity order is 5 > 4 > 2.

The greater reactivity of 1-(5-thiazolyl)ethyl chlo-

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

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(12) These values refer to replacement of the benzene ring by a thiazole ring; we have called them replacement σ^+ constants, σ_{Ar}^+; *cf.* D. S. Noyce and R. L. Castenson, *J. Amer. Chem. Soc.*, **95**, 1247 (1973).

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TABLE I

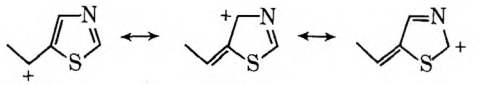
SOLVOLYSIS RATE CONSTANTS FOR 1-ARYLETHYL CHLORIDES IN 80% ETHANOL

Compd solvolyzed	Temp, °C	$10^5 k$, sec^{-1}	Method[a]	Relative rate
1-(5-Thiazolyl)ethyl chloride (3)	25.00	8.55 ± 0.2	A	
	45.00	80.9 ± 0.7	A	174
1-(4-Thiazolyl)ethyl chloride (8)	25.00	0.922 ± 0.02	A	
	45.00	11.5 ± 0.6	A	25
	60.00	46.9 ± 1.0	A	
1-(2-Thiazolyl)ethyl chloride (5)	45.00	0.464[b]		1.00
	60.00	2.29 ± 0.06	B	
	75.00	10.7 ± 0.4	B	
	100.00	88.0 ± 3	C	
1-Phenylethyl chloride	45.00	9.76[c]	A	21

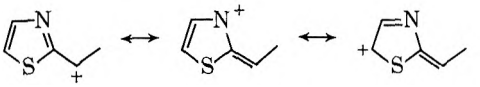
[a] A, constant pH: B, aliquot; C, sealed ampoules. [b] Extrapolated from data at higher temperatures. [c] Determined by B. Bartman; agrees well with values reported by V. J. Shiner, W. E. Buddenbaum, B. L. Murr, and G. Lamaty, *J. Amer. Chem. Soc.*, 90, 418 (1968).

ride (3) compared to 1-(4-thiazolyl)ethyl chloride (8) is in accord with the generally more facile electrophilic reactions of the 2 position in thiophene than of the 3 position in thiophene.[6] The reactivity ratio is sharply reduced in the case of the thiazole compounds. The comparison of 1-(5-thiazolyl)ethyl chloride (3) with 1-(2-thiazolyl)ethyl chloride (5) reflects the deleterious influence of replacing one of the carbons by nitrogen, as shown by considering the contributing canonical forms for the two cations A and B, where in B one of the forms places electron deficiency directly on the nitrogen. This is reminiscent of the comparison of 3-pyridyl systems with 2-pyridyl systems.

The various calculations summarized by Metzger, *et al.*,[14] do not agree about the reactivity of the thiazoles relative to benzene. Our data provide a direct



(A)



(B)

experimental evaluation of this relationship. There are relatively limited data on aromatic substitution reactions with which to make comparison. The acetoxymercuration of various thiazoles has suggested the reactivity order 5 > 4 > 2;[15] direct comparison with benzene is not available. Some systems have been studied which allow indirect comparison in competitive situations. Though the nitration of the various phenylthiazoles[16] gives products resulting from nitration in the benzene ring, bromination of 4-chloro-2-phenylthiazole occurs in the thiazole ring.[17] These results are in accord with our reactivity sequence.

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(16) *Cf.* R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," Wiley, New York, N. Y., 1967, p 321.

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Experimental Section[18]

1-(2-Chloro-5-thiazolyl)ethanol (1).—To a stirred solution of dry ether (100 ml) at −80° under a nitrogen atmosphere was added 2-chlorothiazole (9.81 g, 0.082 mol) in 75 ml of ether. Simultaneously from another dropping funnel, precooled *n*-butyllithium (0.09 mol, 55.8 ml) in hexane was added. After the 1-hr addition period, the light tan solution was stirred for 2.5 hr with gradual warming to −20°. Acetaldehyde (17.0 ml, 0.30 mol) was rapidly added. The solution was stirred for 1 hr and then quenched with 100 ml of cold water. The layers were separated and the aqueous layer was exrracted with 3 × 30 ml of ether. The combined ether layers were dried ($MgSO_4$) and filtered. Distillation afforded 11.76 g (88%) of alcohol 1: bp 173° (51 mm); nmr ($CDCl_3$) δ 1.55 (d, 3, J = 6.5 Hz, $CHCH_3$), 4.73 (s, 1, CHOH), 5.03 (q, 1, J = 6.5 Hz, $CHCH_3$), 7.22 (s, 1, 4-H).

1-(5-Thiazolyl)ethanol (2),—A solution of 1-(2-chloro-5-thiazolyl)ethanol (10.0 g) in 50 ml of acetic acid was stirred with heating to near boiling before adding zinc dust (8.0 g). The reaction mixture was refluxed for 4 hr. The resulting solution was diluted with 100 ml of ether and adjusted to pH 8 by the slow addition of ammonium hydroxide. The layers were then separated, and the aqueous layer was extracted with 3 × 40 ml of ether. The combined ether extracts were dried over anhydrous magnesium sulfate and filtered. Removal of the ether on a rotary evaporator gave a yellow liquid which had spectral properties indicating a 50:50 mixture of the desired alcohol 2 and its acetate. The acetate was hydrolyzed by heating this mixture for 2 hr under reflux with 150 ml of 1 *N* HCl. After cooling, the solution was diluted with 200 ml of ether and neutralized. The layers were separated and the aqueous layer was extracted with 3 × 30 ml of ether. The combined extracts were dried ($MgSO_4$), filtered, and distilled to give 3.97 g (50%) of alcohol 2: bp 126–128° (25 mm); nmr ($CDCl_3$) δ 1.55 (d, 3, J = 6.5 Hz, $CHCH_3$), 4.70 (s, 1, OH), 5.12 (q, 1, J = 6.5 Hz, $CHCH_3$), 7.53 (s, 1, 4-H), 8.62 (s, 1, 2-H).

Anal. Calcd for C_5H_7NOS: C, 46.49; H, 5.46; N, 10.84; S, 24.82. Found: C, 46.54; H, 5.36; N, 11.02; S, 24.64.

1-(5-Thiazolyl)ethyl Chloride (3).—A stirred solution of 1-(5-thiazolyl)ethanol (3.5 g) in 50 ml of cargon tetrachloride was treated under nitrogen with phosphorus pentachloride (5.64 g) for 2 hr. After the volume was reduced to approximately 10 ml on a rotary evaporator, the solution was diluted with 100 ml of ether and stirred for 20 min with a 5-ml aqueous slurry of sodium bicarbonate. The resulting layers were separated, and the organic layer was dried ($MgSO_4$), filtered, and concentrated. The resulting light yellow oil was further purified by chromatography on silica gel. Elution with 95% hexene–5% ether resulted in 2.35 g (67%) of the pure chloride 3: nmr ($CDCl_3$) δ 1.90 (d, 3, $J_{CH.CH_3}$ = 6.7 Hz, $CHCH_3$), 5.33 (q, 1, $J_{CH.CH_3}$ = 6.7 Hz, CHCl), 7.75 (s, 1, 4-H), 8.73 (s, 1, 2-H).

Anal. Calcd for C_5H_6ClNS: C, 40.68; H, 4.09; Cl, 24.02; N, 9.49. Found: 40.78; H, 3.94; Cl, 24.28; N, 9.62.

1-(2-Thiazolyl)ethanol (4).—Halogen–metal interchange between 2-bromothiazole and butyllithium at −80° was followed by addition of a threefold excess of acezaldehyde. Isolation in the usual manner and distillaton afforded 4 in 51% yield: bp 115–116° (26 mm) [lit.[19] bp 112–115° (13–15 mm)]; nmr (CCl_4) δ 1.48 (d, 3, J = 7.0 Hz, $CHCH_3$), 5.05 (q, 1, J = 7.0 Hz, $CHCH_3$), 5.70 (s, 1, OH), 7.13 (d, 1, $J_{4,5}$ = 3.5 Hz, 5-H), 7.50 (d, 1, $J_{4,5}$ = 3.5 Hz, 4-H).

1-(2-Thiazolyl)ethyl Chloride (5).—Conversion of alcohol 4 to the chloride 5 was accomplished using thionyl chloride. Workup and distillation afforded 42% of the chloride 5: bp 84–85° (36 mm); nmr ($CDCl_3$) δ 1.90 (d, 3, J = 7.0 Hz, $CHCH_3$), 5.35 (q, 1, J = 7.0 Hz, CHCl), 7.25 (d, 1, J = 3.5 Hz, 5-H), 7.67 (d, 1, J = 3.5 Hz, 4-H).

Anal. Calcd for C_5H_6ClNS: C, 40.68; H, 4.09; Cl, 24.02; N, 9.49; S, 21.72. Found: C, 40.50; H, 4.07; Cl, 23.98; N, 9.60; S, 21.53.

4-Formylthiazole (6).—The procedure used was a modifica-

(18) Melting points and boiling points are uncorrected. Routine infrared spectra were obtained using a Perkin-Elmer Infracord Model 237. Nmr spectra were obtained using either a Varian A-60 or a Varian T-60 spectrometer. Analyses are by the Chemical Analytical Services Laboratory, College of Chemistry, University of California, Berkeley, Calif. 94720.

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tion of that of Baganz and Rüger.[20] Thioformamide[21] and tribromoacetone[22] were combined in ether and kept cold for 2 days, and the resulting solid was thoroughly washed to give 4-dibromomethyl-4-hydroxy-Δ^2-thiazoline hydrobromide, mp 120–123°. Following Baganz and Rüger,[20] the hydrobromide was treated with sulfuric acid to give 4-dibromomethylthiazole, mp 89–90° (hexane), which was hydrolyzed to 6: mp 59–61° (lit.[23] 65–66°); nmr ($CDCl_3$) δ 8.31 (d, 1, $J_{2,5}$ = 1.9 Hz, 5-H), 8.98 (d, 1, $J_{2,5}$ = 1.9 Hz, 2-H), 10.13 (s, 1, CHO).

1-(4-Thiazolyl)ethanol (7).—Treatment of 6 with methylmagnesium bromide gave 90% of the alcohol 7: bp 164–165° (55 mm); nmr ($CDCl_3$) δ 1.57 (d, 3, J = 6.3 Hz, $CHCH_3$), 4.08 (s, 1, CHOH), 5.05 (q, 1, J = 6.3 Hz, $CHCH_3$), 7.20 (d, 1, $J_{2,5}$ = 1.9 Hz, 5-H), 8.53 (d, 1, $J_{2,5}$ = 1.9 Hz, 2-H).

1-(4-Thiazolyl)ethyl Chloride (8).—Alcohol 7 was converted to chloride 8 using phosphorus pentachloride in 74% yield: nmr ($CDCl_3$) δ 1.90 (d, 3, J = 6.8 Hz, $CHCH_3$), 5.28 (q, 1, J = 6.8 Hz, $CHCH_3$), 7.32 (d, 1, $J_{2,5}$ = 2.0 Hz, 5-H), 8.75 (d, 1, $J_{2,5}$ = 2.0 Hz, 2-H). Decomposition occurs on attempted distillation.

Anal. Calcd for C_5H_6ClNS: C, 40.68; H, 4.09; Cl, 24.02; N, 9.49. Found: C, 40.82; H, 4.33; Cl, 24.22; N, 9.28.

Kinetic Procedures.—Absolute ethanol was prepared by the method of Lund and Bjerrum.[24] Four volumes of absolute ethanol were diluted with one volume of water. Rate constants were determined in three different fashions. Method A was by maintenance of a static pH. This method is particularly convenient when measurements are made near room temperature and half-lives are reasonably short. A Radiometer automatic titration apparatus was used, consisting of a no. TTT 1c automatic titrator, a no. ABU 1c autoburet (with a 2.5-ml buret), a TTA 3c titrator assembly, and a no. SBR 2c recorder. A 49-ml sample of the reaction medium was brought to temperature in the reaction cell in a constant-temperature bath. Reaction was initiated by injecting, *via* syringe, *ca.* 0.0005 mol of substrate dissolved in 1 ml of 80% ethanol–20% water into the reaction cell. The reaction solution was maintained at a constant apparent pH of 7.5 by the automatic addition of 0.30 *M* potassium hydroxide in 80% ethanol. The recorder plotted a continuous curve of the addition of base *vs.* time.

Alternatively, standard aliquot techniques (method B) or sealed ampoules (method C) were used. First-order rate constants were computed using the nonlinear least squares program, LSKIN 1.[25]

Registry No.—1, 40982-18-1; 2, 41040-84-0; 3, 41040-85-1; 4, 40982-30-7; 5, 40982-31-8; 6, 3364-80-5; 7, 41040-89-5; 8, 3364-77-0; 2-chlorothiazole, 3034-52-4; acetaldehyde, 75-07-0; 2-bromothiazole, 3034-53-5; thioformamide, 115-08-2; tribromoacetone, 3770-98-7; 4-dibromomethyl-4-hydroxy-Δ^2-thiazoline hydrobromide, 41040-92-0; 4-dibromomethylthiazole, 41040-93-1; methyl bromide, 74-83-9.

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Transmission of Substituent Effects in Heterocyclic Systems. Rates of Solvolysis of Substituted Thiazolylethanol Derivatives[1,2]

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Received April 3, 1973

The rates of solvolysis for several substituted 1-(5-thiazolyl)ethanol derivatives have been measured in 80% ethanol and are compared with similar studies on other heterocycles. For the group 1-(2-X-5-thiazolyl)ethyl chlorides, reaction rates are well correlated by σ_p^+ for the substituents X. Similar correlation is observed for the solvolysis rates of 1-(5-X-2-thiazolyl)ethyl chlorides. These results are discussed in terms of the application of molecular orbital calculations relevant to the thiazole system.

In continuing studies from these laboratories[2–6] on the modes of transmission of substituent effects in heteocyclic systems, we have examined the relative reactivities of a number of substituted thiazoles.

There have been a few previous investigations of the application of the Hammett equation to thiazole derivatives. Imoto, Otsuji, and coworkers[7,8] have measured saponification rates for substituted ethyl thiazolecarboxylates and the dissociation constants of the corresponding acids. Moderately satisfactory correlation with Hammett σ values was observed; however, the value of ρ was occasionally surprising.

Our previous studies have shown that the solvolysis reaction is a useful probe for examination of heterocyclic systems[4,9] and that reactivities can often be related to parameters obtained from molecular orbital calculations. Metzger, *et al.*,[10] have recently summarized the results of a number of different molecular orbital calculations on thiazole. All of the various levels of approximation agree that the susceptibility to electrophilic aromatic substitution is in the order position 5 > position 4 > position 2; however, there is not agreement as to reactivity relative to benzene. Our studies[2] have shown that the order relative to benzene is 5-thiazolyl > 4-thiazolyl $\simeq$ phenyl > 2-thiazolyl.

Effect of Substituents.—We have prepared a number of 2-substituted 1-(5-thiazolyl)ethanols (A), and have measured the rates of solvolysis of the respective chlorides or *p*-nitrobenzoates. The large differences in reactivity dictated the use of different leaving groups. A pair of 5-substituted 1-(2-thiazolyl)ethanols (B) has likewise been examined.

In the case of series A, the measured rates are col-

(1) Supported in part by a grant from the National Science Foundation, GP-6133X.
(2) Previous paper: D. S. Noyce and S. A. Fike, *J. Org. Chem.*, **38**, 3316 (1973).
(3) D. S. Noyce and R. W. Nichols, *J. Org. Chem.*, **37**, 4306, 4311 (1972).
(4) D. A. Forsyth and D. S. Noyce, *Tetrahedron Lett.*, 3893 (1972).
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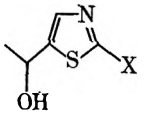
(6) D. S. Noyce and C. A. Lipinski, *J. Org. Chem.*, **37**, 2615 (1972).
(7) E. Imoto and Y. Otsuji, *Bull. Univ. Osaka Prefect., Ser. A*, **6**, 115 (1958); *Chem. Abstr.*, **53**, 3027*h* (1959).
(8) Y. Otsuji, T. Kimura, Y. Sugimoto, E. Imoto, Y. Omori, and T. Okawara, *Nippon Kagaku Zasshi*, **80**, 1024, 1297 (1959).
(9) D. S. Noyce and R. W. Nichols, *Tetrahedron Lett.*, 3889 (1972).
(10) R. Phan-Tan-Luu, L. Bouscasse, E. Vincent, and J. Metzger, *Bull. Soc. Chim. Fr.*, 1149 (1969).

TABLE I

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

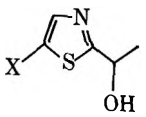
Compd solvolyzed	Leaving group	Kinetic[a] method	T, °C	10^5k, sec^{-1}	σ^+[b]	Rel rates
4 (H)	Cl	1 and 3	45.00	80.9 ± 0.7[c]	0.00	1.00
2 (2-Cl)	Cl	1 and 3	25.00	2.25 ± 0.1	0.114	
		1 and 3	45.00	23.4 ± 0.5		0.29
		1	60.00	95.0		
7 (2-CH_3)	Cl	3	25.00	385 ± 10		
6	OPNB		25.00	0.001[d]		
7	Cl		45.00	6070[e]	−0.311	75
6	OPNB	2	75.00	0.558 ± 0.007		
		2	110.00	17.2 ± 0.5		
10 (2-SCH_3)	OPNB	2	45.00	1.88 ± 0.04		
	OPNB	1	75.00	40.9		
	Cl		45.00	79,700[e]	−0.604	9,800
13 (2-OCH_3)	OPNB	1	45	12.9 ± 0.5		
	Cl		45.00	5.5 × 10^6[e]	−0.778	68,000

[a] Kinetic methods have been described previously (ref 3 and 4): 1, the usual aliquot technique; 2, using sealed ampoules; 3, at constant pH. [b] Reference 11. [c] Reference 21. [d] Extrapolated from rates at higher temperatures. [e] Calculated; see text.



A

1, X = Cl
3, X = H
5, X = CH_3
9, X = SCH_3
12, X = OCH_3



B

14, X = H
17, X = CH_3
20, X = SCH_3

lected in Table I. From the rates for 1-(2-methyl-5-thiazolyl)ethyl chloride (6) and 1-(2-methyl-5-thiazolyl)ethyl *p*-nitrobenzoate (7) we calculate a k_{Cl}/k_{OPNB} rate ratio of 3.8×10^5. Consideration of other compounds where k_{Cl}/k_{OPNB} ratios are available suggests using $k_{Cl}/k_{OPNB} = 4.25 \times 10^5$. This ratio has been used to construct a relative sequence at 45° (column 7, Table I). A plot of these data against Brown's σ_p^+ substituent constants[11] gives a very high quality correlation (c.c = 0.998) and a ρ of −6.2.

Recently, Forsyth and Noyce[4] have pointed out that rate correlations for a number of heterocyclic systems are excellent with σ_p^+ in strictly defined and limited structural situations. In those cases where there is direct conjugation in the classical valence bond representation between the developing carbonium ion site and the site of attachment of the substituent, the correlation with Brown's electrophilic subtituent constants,[11] σ_p^+, is excellent; further, the magnitude of ρ is directly related to charge distribution as determined from CNDO/2 calculations.[4] This generalization manifested itself in furans, benzofurans, thiophenes, and here in thiazole.

To further extend these observations we have examined a limited number of 5-substituted 1-(2-thiazolyl)ethanol derivatives (series B).

The measured rate data are given in Table II, and relative rates are tabulated in column 7 of Table II. These data are very smoothly correlated also with σ_p^+ substituent constants. The value of ρ as determined from these three compounds (5, 13, 17) is −6.26. This value of ρ is very similar to that obtained for series A. This fact is in accord with the very similar values

(11) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4079 (1958).

TABLE II

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

Compd solvolyzed	Leaving group	Kinetic[a] method	T, °C	10^5k, sec^{-1}	σ^+[b]	Rel rates
15 (5-H)	Cl		45.00	0.464[c]	0.00	1.00
18 (5-CH_3)	Cl	1	45.00	34.4 ± 0.7	−0.311	74
21 (5-SCH_3)	Cl	3	0.00	31.3 ± 0.8		
		3	25.00	452 ± 4		
			45.00	2830[d]	−0.604	6100

[a] See footoote *a*, Table I. [b] Reference 11. [c] Reference 2. [d] Extrapolated from data at lower temperatures.

of the changes in regional charge, Δq, calculated for these two isomeric thiazole moieties.[3,4]

Thus, in those limited siutations where direct conjugation, in a classical valence bond sense, is permissible, substituent constants from benzene appear applicable to substituted thiazoles.

Experimental Section[12]

1-(2-Chloro-5-thiazolyl)ethanol (1) has been reported previously.[2]

1-(2-Chloro-5-thiazolyl)ethyl Chloride (2).—Thionyl chloride (36 ml) was stirred at 0° in an ice bath while 1-(2-chloro-5-thiazolyl)ethanol (5.54 g) in 10 ml of dry ether was slowly added. After being stirred for 0.5 hr, the bath was removed and stirring was continued for an additional 1 hr. After reducing the volume of 15 ml on a rotary evaporator, the remaining solution was diluted with 100 ml of water. The stirred solution was brought to pH 9 by the slow addition of 1 *N* sodium hydroxide. The layers were separate and the aqueous layer was extracted with 2 × 30 ml of ether. The combined ether layers were then washed with 50 ml of 0.05 *N* sodium hydroxide, dried over anhydrous magnesium sulfate, and filtered. Removal of the ether on a rotary evaporator gave a yellow oil which was distilled to yield 3.19 g (52%) of the pure chloride 2: bp 150° (75 mm); nmr ($CDCl_3$) δ 1.88 (d, 3, *J* = 7.0 Hz, $CHCH_3$), 5.29 (q, 1, *J* = 7.0 Hz, CHCl), 7.64 (s, 1, 4-H).

Anal. Calcd for $C_5H_5Cl_2NS$: C, 32.98; H, 2.77; N, 7.69; S, 17.61. Found: C, 33.12; H, 2.58; N, 7.88; S, 17.45.

1-(5-Thiazolyl)ethanol (3) and **1-(5-thiazolyl)ethyl chloride** (4) have been reported.[2]

1-(2-Methyl-5-thiazolyl)ethanol (5).—Ether (100 ml) was

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

stirred at 0°[13] under a nitrogen atmosphere while 2-methylthiazole[16] (6.0 g, 0.06 mol) in 50 ml of ether was added dropwise from a dropping funnel. Simultaneously, *n*-butyllithium (0.066 mol, 41 ml in hexane) was added from a second dropping funnel. The thiazole was kept in slight excess during the 40-min addition period. After the addition was complete, the golden solution was stirred for an additional 15 min. Acetaldehyde (11.35 ml, 0.20 mol) was rapidly added, and an exothermic reaction ensued which resulted in a short period of gentle reflux. The ice bath was removed, and the solution was stirred for 15 min before quenching with 125 ml of cold water. The two layers were separated, and the aqueous layer was extracted with 3 × 50 ml of methylene chloride. The combined organic layers were dried over anhydrous magnesium sulfate and filtered. Removal of the solvent on a rotary evaporator yielded 8.33 g g (97%) of a crude yellow oil having excellent spectral properties for the alcohol **5** and essentially free of the isomeric 1-(2-thiazolyl)propan-2-ol: bp 89.5–90.0° (0.1 mm);[17] nmr ($CDCl_3$) δ 1.53 (d, 3, J = 6.5 Hz, $CHCH_3$), 2.60 (s, 3, 2-CH_3), 5.05 (q, 1, J = 6.5 Hz, $CHCH_3$), 5.50 (s, 1, OH), 7.30 (s, 1, 4-H).

1-(2-Methyl-5-thiazolyl)ethyl *p*-nitrobenzoate (6) was prepared in the usual way by treating the lithium salt of **5** with *p*-nitrobenzoyl chloride. The ester **6** was purified by chromatography on silica gel: mp 49–50°; nmr ($CDCl_3$) δ 1.82 (d, 3, J = 6.7 Hz, $CHCH_3$), 2.68 (s, 3, 2-CH_3), 6.42 (q, 1, J = 6.7 Hz, $CHCH_3$), 7.67 (s, 1, 4-H), 8.20 (s, 4, phenyl H).

Anal. Calcd for $C_{13}H_{12}N_2O_4S$: C, 53.41; H, 4.14; N, 9.58; S, 10.97. Found: C, 53.45; 4.11; N, 9.52; S, 10.69.

1-(2-Methyl-5-thiazolyl)ethyl chloride (7) was prepared by treating the alcohol **5** with phosphorus pentachloride in methylene chloride. Work up in the usual manner yielded 2.3 g (75%) of a light yellow oil which was eluted from a 20-cm column of silica gel with 1 l. of hexane to give the pure chloride **7**: nmr ($CDCl_3$) δ 1.83 (d, 3, J = 6.5 Hz, $CHCH_3$), 2.60 (s, 3, 2-CH_3), 5.22 (q, 1, J = 6.5 Hz, $CHCH_3$), 7.38 (s, 1, 4-H).

Anal. Calcd for C_6H_8ClNS: C, 44.58; H, 4.99; Cl, 21.93; N, 8.66. Found: C, 44.79; H, 5.05; Cl, 21.78; N, 8.77.

2-Methylthiothiazole (8).—Methyl mercaptan (16 ml) was added to 1 equiv of sodium methoxide in methanol (200 ml) at 0°. 2-Chlorothiazole (17.6 g) was added with 0.01 g of potassium iodide. After heating under reflux for 18 hr, the reaction mixture was diluted with water (400 ml) and extracted with ether. The ethereal extracts were dried ($MgSO_4$) and distilled to afford **8**: a colorless oil; 14.3 g, 74%; bp 89–90° (5 mm) [lit.[18] 68° (2 mm)]; nmr ($CDCl_3$) δ 2.66 (s, 3, SCH_3), 7.12 (d, 1, $J_{4,5}$ = 3.4 Hz, 5-H), 7.57 (d, 1, $J_{4,5}$ = 3.4 Hz, 4-H).

1-(2-Methylthio-5-thiazolyl)ethanol (9).—2-Methylthiothiazole (13.1 g, 0.1 mol) was metalated with *n*-butyllithium at 0°. Work-up in the usual fashion afforded 10.9 g (63%) of slightly impure alcohol **9**. This was further purified by elution through a 30-cm silica gel column with 1 l. of 70% hexane–30% ether: bp 174–180° (5 mm); nmr ($CDCl_3$) δ 1.51 (d, 3, J = 6.3 Hz, $CHCH_3$), 2.61 (s, 3, SCH_3), 4.97 (s, 1, OH), 5.05 (q, 1, J = 6.3 Hz, $CHCH_3$), 7.27 (s, 1, 4-H).

Anal. Calcd for $C_6H_9NOS_2$: C, 41.11; H, 5.18; N, 8.00; S, 36.58. Found: C, 41.02; H, 5.07; N, 7.92; S, 36.60.

1-(2-Methylthio-5-thiazolyl)ethyl *p*-nitrobenzoate (10) was prepared by treating the lithium salt of **9** with *p*-nitrobenzoyl chloride. The crude **10** was recrystallized from hexane to give a pure sample: mp 90.5–91.0°; nmr ($CDCl_3$) δ 1.80 (d, 3, J = 6.6 Hz, $CHCH_3$), 2.67 (s, 3, SCH_3), 6.33 (q, 1, J = 6.6 Hz, $CHCH_3$), 7.60 (s, 1, 4-H), 8.18 (s, 4, nitrophenyl H).

Anal. Calcd for $C_{13}H_{12}N_2O_4S_2$: C, 48.14; H, 3.73; N, 8.63; S, 19.77. Found: C, 48.22; H, 3.85; N, 8.56; g, 19.62.

2-Methoxythiazole (11).—The procedure used was a modification of that devised by Gronowitz for the synthesis of 5-methoxythiazole.[19]

Potassium iodide (0.01 g), cupric oxide (3.73 g, 0.0466 mol), and 2-chlorothiazole (10.0 g, 0.084 mol) were added to a solution of sodium (6.0 g, 0.26 mol) in 75 ml of anhydrous methanol. The mixture was stirred at reflux for 2 hr before cooling. The resulting dark solution was filtered, diluted with an equal volume of water, and then extracted with 3 × 40 ml of ether. The combined ether layers were dried ($MgSO_4$) distilled to give 4.76 g (50%) of pure 2-methoxythiazole: bp 49–50° (17 mm); ir (neat) 2950, 1535, 1475, 1240; 1190 cm^{-1}; nmr ($CDCl_3$) δ 4.00 (s, 3, OCH_3), 6.55 (d, 1, $J_{4,5}$ = 3.85 Hz, 5-H), 7.01 (d, 1, $J_{4,5}$ = 3.85 Hz, 4-H).

Anal. Calcd for C_4H_5NOS: C, 41.72; H, 4.38; N, 12.16 Found: C, 41.52; H, 4.51; N, 11.99.

1-(2-Methoxy-5-thiazolyl)ethanol (12).—Metalation of **11** was carried out at 0°. After 10 min a threefold excess of acetaldehyde was added. Work-up in the usual fashion gave 2.3 g (35%) of the clear, liquid alcohol **12**: bp 144° (19 mm); nmr ($CDCl_3$) δ 1.50 (d, 3, J_{CH,CH_3} = 6.8 Hz, $CHCH_3$), 3.96 (s, 3, OCH_3), 4.08 (s, 1, OH), 4.90 (q, 1, J_{CH,CH_3} = 6.8 Hz, $CHCH_3$), 6.80 (s, 1, 4-H),

1-(2-Methoxy-5-thiazolyl)ethyl *p*-nitropenzoate (13) was prepared in the usual fashion in 51% yield: mp 96–97°; nmr ($CDCl_3$) δ 1.75 (d, 3, $CHCH_3$), 4.03 (s, 3, OCH_3), 5.25 (q, 1, J = 6.8 Hz, $CHCH_3$), 7.13 (s, 1, 4-H), 8.17 (s, 4, nitrophenyl H).

1-(2-Thiazolyl)ethanol (14) has been reported.[2,20]

1-(2-Thiazolyl)ethyl Chloride (15).—Conversion of alcohol **14** to the chloride **15** was accomplished using thionyl chloride. Work-up and distillation afforded 42% chloride **15**: bp 84–85° (36 mm); nmr ($CDCl_3$) δ 1.90 (d, 3), 535 (q, 1), 7.25 (d, 1), 7.67 (d, 1).

Anal. Calcd for C_5H_6ClNS: C, 40.68; H, 4.09; Cl, 24.02; N, 9.49; S, 21.72. Found: C, 40.50; H, 4.07; Cl, 23.98; N, 9.60; S, 21.53.

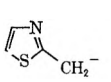
5-Methylthiazole (16).—Metalation of 2-chlorothiazole with butyllithium at −45°, followed by treatment with methyl iodide, gave a mixture of 2-chlorothiazole and 2-chloro-5-methylthiazole.[21]

This mixture (14.5 g 50:50 by nmr) was directly reduced by a procedure similar to that used by McLean and Muir for the reduction of 2-chlorothiazole.[22] The mixture (14.5 g) in 50 ml of glacial acetic acid was stirred with heating. When the temperature reached 60°, zinc dust (15.0 g, 0.23 g-atom) was added. The solution was heated under reflux for 4 hr and cooled. The resulting solution was neutralized with dilute ammonium hydroxide and steam distilled. The first 100 ml of distillate was extracted with 3 × 30 ml of ether. The combined ether extracts were dried ($MgSO_4$) and concentrated giving 6.82 g of the mixture. The mixture was separated on a spinning-band column by distilling the thiazole at atmospheric pressure then reducing the pressure to distil the remaining 5-methylthiazole to give 3.0 g (55%) of pure 5-methylthiazole (**16**): bp 64–66° (25 mm) [lit.[23] bp 70–72° (41 mm)]; nmr ($CDCl_3$) δ 2.42 (d, 3, $J_{4\text{-H},5\text{-}CH_3}$ = 1.2 Hz, 5-CH_3), 7.55 (q, 1, $J_{4\text{-H},5\text{-}CH_3}$ = 1.2 Hz, 4-H, incompletely resolved), 8.60 (s, 1, 2-H).

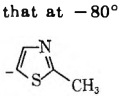
1-(5-Methyl-2-thiazolyl)ethanol (17).—Metalation of 5-methylthiazole at −80° using butyllithium was followed by addition of a threefold excess of acetaldehyde. Work-up in the usual fashion afforded alcohol **17** in 49% yield: bp 124–126° (5 mm); nmr (CCl_4) δ 1.54 (d, 3, J_{CH,CH_3} = 6.5 Hz, $CHCH_3$), 2.40 (d, 3, $J_{4\text{-H},5\text{-}CH_3}$ = 1.7 Hz, 5-CH_3), 4.90 (s, 1, OH), 5.06 (q, 1, J_{CH,CH_3} = 6.5 Hz, $CHCH_3$), 7.26 (q, 1, $J_{4\text{-H},5\text{-}CH_3}$ = 1.7 Hz, 4-H).

Anal. Calcd for C_6H_9NOS: C, 50.32; H, 6.34; N, 9.78; S, 22.39. Found: C, 50.50; H, 6.36; N, 9.51; S, 22.32.

(13) The reaction of 2-methylthiazole with a strong base has two major modes of reaction. A methyl proton can be removed which will form the reactive ion i, or the most reactive ring proton can be removed which will form the reactive ion ii. We have observed that at −80° *n*-butyllithium



i



ii

reacts with 2-methylthiazole to yield a mixture of anions which further reacts with acetaldehyde to give a mixture of products (42% through i and 58% through ii by nmr). On the other hand, at 0° at least 95% of the reaction goes through ring proton abstraction to give products from ion ii. This work agrees well with the trend reported by Crousier and Metzger[14] on similar studies involving reaction of i and ii with methyl iodide. The situation is very complex as shown by the recent studies of Meyers and Knaus.[15]

(14) J. Crousier and J. Metzger, *Bull. Soc. Chim. Fr.*, 4134 (1964).

(15) A. I. Meyers and G. N. Knaus, *J. Amer. Chem. Soc.*, **95**, 3408 (1973).

(16) A. Hantzsch, *Justus Liebigs Ann. Chem.*, **250**, 257 (1899).

(17) Crousier and Metzger[14] report a 6:1 mixture of **5** and 1-(2-thiazolyl)propan-2-ol, bp 132–134° (11 mm), and the nmr spectra of both isomers from reaction of butyllithium and 2-methylthiazole at −60°.

(18) P. Bastianelli, M. Chanon, and J. Metzger, *Bull. Soc. Chim. Fr.*, 1948 (1967).

(19) G. Borgen, S. Gronowitz, R. Dahlbom, and B. Holmberg, *Acta Chem. Scand.*, **20**, 2539 (1966).

(20) J. Beraud and J. Metzger, *Bull. Soc. Chim. Fr.*, 2072 (1962).

(21) The studies of Crousier and Metzger[14] indicate that incomplete alkylation is not surprising.

(22) J. McLean and G. D. Muir, *J. Chem. Soc.*, 383 (1942).

(23) H. Erlenmeyer and P. Schmidt, *Helv. Chim. Acta*, **29**, 1957 (1946).

1-(5-Methyl-2-thiazolyl)ethyl Chloride (18).—This chloride was prepared from alcohol 16 using phosphorus pentachloride to give a 67% yield of crude 18. This was further purified by chromatography on silica gel to give 54% colorless chloride 18: nmr ($CDCl_3$) δ 1.91 (d, 3, $J_{CH.CH_3}$ = 7.0 Hz, $CHCH_3$), 2.41 (d, 3, $J_{4\text{-}H,5\ CH_3}$ = 1.1 Hz, 5-CH_3), 5.27 (q, 1, $J_{CH.CH_3}$ = 7.0 Hz, $CHCH_3$), 7.33 (q, 1, $J_{4\text{-}H,5\text{-}CH_3}$ = 1.1 Hz, 4-H).

Anal. Calcd for C_6H_8ClNS: C, 44.58; H, 4.99; Cl, 21.93; N, 8.66; S, 19.84. Found: C, 44.43; H, 5.01; Cl, 21.94; N, 8.73; S, 19.74.

5-Methylthiothiazole (19).—Methyl mercaptan (27.7 ml, 0.5 mol) was added to 1 equiv of sodium methoxide in 175 ml of methanol at 0°. 5-Bromothiazole (32.8 g, 0.2 mol)[24] and 0.01 g of potassium iodide were added, and the solution was heated under reflux for 5 hr. The resulting clear solution and white precipitate wee taken up in 100 ml of water. The aqueous solution was then extracted with 3 × 200 ml of ether. The combined ether layers were dried ($MgSO_4$) and concentrated to give an oil which was distilled under reduced pressure to give 6.85 g (26%) of pure 5-methylthiothiazole (19): bp 132–134° (50 mm); nmr ($CDCl_3$) δ 2.47 (s, 3, SCH_3), 7.75 (s, 1, 4-H), 8.82 (s, 1, 2-H).

Anal. Calcd for $C_4H_5NS_2$: C, 36.61; H, 3.85; S, 48.93. Found: C, 36.76; H, 4.07; S, 49.10.

(24) H. C. Beyerman, P. H. Berben, and J. S. Bontekoe, *Recl. Trav. Chim., Pays-Bas*, **73**, 325 (1954).

1-(5-Methylthio-2-thiazolyl)ethanol (20).—Metalation of 18 with butyllithium at −80° and addition of a threefold excess of acetaldehyde afforded crude 20. Distillation afforded pure 20 in 79% yield: bp 106.0–106.5° (0.2 mm); nmr ($CDCl_3$) δ 1.58 (d, 3, J = 6.2 Hz, $CHCH_3$), 2.45 (s, 3, SCH_3), 5.02 (s, 1, OH), 5.02 (q, 1, J = 6.2 Hz, $CHCH_3$), 7.42 (s, 1, 4-H).

Anal. Calcd for $C_6H_9NOS_2$: C, 41.12; H, 5.18; S, 36.59. Found: C, 41.03; H, 5.09; S, 36.32.

1-(5-Methylthio-2-thiazolyl)ethyl Chloride (21).—Treatment of 20 with phosphorus pentachloride in methylene chloride and isolation gave 21 in 96% yield as a light yellow oil. Further purification to obtain a sample for kinetic studies was accomplished by chromatography on silica gel: nmr ($CDCl_3$) δ 1.92 (d, 3, J = 6.7 Hz, $CHCH_3$), 2.48 (s, 3, SCH_3), 5.25 (q, 1, J = 6.7 Hz, $CHCH_3$), 7.53 (s, 1, 4-H).

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

Registry No.—1, 40982-18-1; 2, 40982-19-2; 5, 20155-81-1; 5 lithium salt, 40982-21-6; 6, 40982-22-7; 7, 40982-23-8; 8, 5053-24-7; 9, 40982-25-0; 9 lithium salt, 40982-26-1; 10, 40982-27-2; 11, 14542-13-3; 12, 40982-28-3; 13, 40982-29-4; 14, 40982-30-7; 15, 40982-31-8; 16, 3581-89-3; 17, 40982-32-9; 18, 40982-33-0; 19, 40982-34-1; 20, 40982-35-2; 21, 40982-36-3; 2-methylthiazole, 3581-87-1; acetaldehyde, 75-07-0; *p*-nitrobenzoyl chloride, 122-04-3; methyl mercaptan, 74-93-1; 2-chlorothiazole, 3034-52-4; 5-bromothiazole, 3034-55-7.

Transmission of Substituent Effects in Heterocyclic Systems. Rates of Solvolysis of Substituted 1-(4-Thiazolyl)ethyl Chlorides[1,2]

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Received April 3, 1973

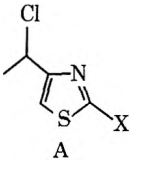
Electrophilic substituent constants, σ_m^+, have been found unacceptable for correlating the relative rates of solvolysis of 1-(2-substituted 4-thiazolyl)ethyl chlorides in 80% ethanol. Likewise, σ_m is also unsatisfactory. These data are discussed in light of several other heterocyclic systems, where similarly poor correlations have been found. It is suggested that judicious comparison of appropriately substituted pyridines and thiazoles provides an excellent working model for treatment of these substituent effects. Limited results on the rates of solvolysis of 1-(4-substituted 2-thiazolyl)ethyl chlorides support these conclusions.

This paper reports an examination of the effectiveness of substituents in promoting the solvolysis reaction of 1-(4-thiazolyl)ethyl chloride. This system is of particular interest as it relates to other five-membered heterocyclic systems and the failure of electrophilic substituent constants to reproduce adequately relative reactivities when the substituent and the reacting side chain are in a nonconjugating, or "pseudo-meta," relationship.

Earlier papers from these laboratories pointed out that Brown's electrophilic substituent constants,[3] *i.e.*, σ_m^+, do not provide a suitable basis for correlation in analogous furans,[4] benzofurans[5] and benzothiophenes.[6] It is only coincidental that σ_m^+ is satisfactory in the case of thiophene derivatives.[7] Further, σ_m^+ likewise fails to correlate substituent effects on the rate of solvolysis of 6-substituted 2-(2-pyridyl)-2-chloropropanes.[8] It was suggested that an independent set of substituent constants is needed for this structural situation.

Imoto and Otsuji, *et al.*,[9,10] have reported the application of the Hammett equation to the rates of saponification of ethyl 2-substituted 4-thiazolylcarboxylates and, with the dissociation constants of the corresponding acids, they obtained generally good correlations with σ_m except for the 2-amino substituent. It is interesting to note that this was the only substituent they studied with a very strong resonance capability.

We have previously examined a series of 1-(5-thiazolyl)ethanol derivatives,[2,11] and observed that σ_p^+ usefully correlates the relative reactivity of this series. The present results of rate measurements on a series of substituted 1-(4-thiazolyl)ethyl chlorides (A) are



A

2, X = H
4, X = CH_3
7, X = C_6H_5
11, X = Br
14, X = SCH_3

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

(2) Previous paper: D. S. Noyce and S. A. Fike, *J. Org. Chem.*, **38**, 3318 (1973).

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

(4) D. S. Noyce and H. J. Pavez, *J. Org. Chem.*, **37**, 2620, 2623 (1972).

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

(6) D. A. Forsyth and D. S. Noyce, *Tetrahedron Lett.*, 3893 (1972); D. A. Forsyth, Ph.D. dissertation, University of California, Berkeley, 1973.

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

(8) D. S. Noyce and J. A. Virgilio, *J. Org. Chem.*, **38**, 2660 (1973).

(9) E. Imoto and Y. Otsuji, *Bull. Univ. Osaka Prefect. Ser. A.*, **6**, 115 (1958); *Chem. Abstr.*, **53**, 3027*h* (1959).

(10) Y. Otsuji, T. Kimura, Y. Sugimoto, E. Imoto, Y. Omori, and T. Okawara, *Nippon Kagaku Zasshi*, **80**, 1024, 1297 (1959).

(11) D. S. Noyce and S. A. Fike, *J. Org. Chem.*, **38**, 3316 (1973).

given in Table I. Except for 1-(2-bromo-4-thiazolyl)-ethyl chloride (**11**), every substituent is activating.

TABLE I

RATE CONSTANTS FOR SOLVOLYSIS OF SUBSTITUTED 1-(4-THIAZOLYL)ETHYL CHLORIDES IN 80% ETHANOL

Compd solvolyzed	T, °C	10^5k, sec^{-1}	Rel rate	σ_m^+
2 (H)	45.00	11.1 ± 0.3[a]	1.00	
11 (2-Br)	45.00	1.28 ± 0.03	0.11	0.405
	75.00	24.6 ± 0.4		
4 (2-CH_3)	25.00	9.01 ± 0.08		
	45.00	72.3 ± 1	6.29	−0.066
7 (2-C_6H_5)	45.00	28.0 ± 0.5	2.43	+0.109
	60.00	124 ± 3		
	75.00	425		
14 (2-*S*-CH_3)	25	6.70 ± 0.06		
	45	67.2 ± 1	5.85	+0.158
	60	295 ± 4		

[a] Reported previously.[11]

This clearly reveals that application of σ_m^+ would be unsatisfactory, for, as column 5 of Table I shows, both positive and negative substituent constants are involved. Notable, also, is the strongly activating influence of methyl (**4**). The sixfold rate increase is unusual, and is to be contrasted with the effect of a methyl group introduced in the meta position in benzene derivatives. For benzyl systems $k_{m\text{-Me}}/k_H$ ratios are typically near 2.[12] This activation is also reminiscent of what is seen in the furan series for 1-(5-methyl-3-furyl)ethanol and 1-(4-methyl-2-furyl)ethanol derivatives.[4] In those instances a greater preponderance of a resonance component from the substituent was implicated as being responsible for the observed rate acceleration, both from application of CNDO/2 calculations and from consideration of the treatment of Swain and Lupton[13] in terms of $\mathcal{F}$ and $\mathcal{R}$.

With the recognition that σ_m^+ is an unsatisfactory basis for correlation of the observed sequence of reactivities, we have examined several other alternatives for correlating the relative reactivities. Both σ_m^+ and σ_m are clearly unsatisfactory. Interesting from a pragmatic point of view, σ_p is better. The change in regional charge Δq[14] as evaluated from CNDO/2 calculations represents a distinct improvement. However this approach still appears to underestimate the importance of the resonance component of the total substituent effect. However, highly satisfactory results are obtained, resulting in a very good correlation of the present series with reactivities observed for 6-substituted 2-pyridyl systems by Noyce and Virgilio.[8] The common feature of these two families, with the substituent and reacting side chain flanking the –N= nitrogen, merits comment.

It is constructive to further consider this observed relationship in terms of the balance of field ($\mathcal{F}$) and resonance ($\mathcal{R}$) effects. The Swain and Lupton equation (1) encompasses the earlier treatment of Charton[15]

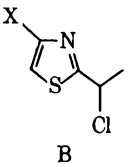
$$\sigma_x = f\mathcal{F} + r\mathcal{R} \quad (1)$$

of substituent influences on dissociation constants of 2-substituted pyridines, which Charton[15] expressed as eq 2.

$$\sigma_T = \lambda\sigma_I + \delta\sigma_R \quad (2)$$

Analysis of the present data in terms of either equation emphasizes the large fractional dependence upon the resonance capabilities of the substituent. In fact the blend of field (inductive) and resonance effects is dominated by resonance effects.

4-Substituted 1-(2-Thiazolyl)ethanol Derivatives (B).—The remaining isomeric family of substituted thiazoles is that represented by structure B. For three



B

15, X = CH_3
17, X = C_6H_5
20, X = H

substituted compounds, **15**, **17**, and **20**, the rates of reaction are given in Table II. Again, the striking

TABLE II

RATE CONSTANTS FOR THE SOLVOLYSIS OF 4-SUBSTITUTED 1-(2-THIAZOLYL)ETHYL CHLORIDES IN 80% ETHANOL

Compd solvolyzed	T, °C	10^5k, sec^{-1}	Rel rate
1-(2-Thiazolyl)ethyl Chloride (**20**)	45.00	0.464[a]	1.00
1-(4-Methyl-2-thiazolyl-ethyl Chloride (**15**)	45.00	5.15 ± 0.2	11.1
	60.00	24.4 ± 1	
	75.00	99.3 ± 3	
1-(4-Phenyl-2-thiazolyl)-ethyl Chloride (**17**)	45.00	1.54 ± 0.05	3.3
	75.00	37.9 ± 0.6	
1-(4,5-Dimethyl-2-thi-azolyl)ethyl Chloride (**19**)	25.00	68 ± 3	
	45.00	593	1275

[a] From ref 11.

activation by methyl (k_{15}/k_{20} = 11) is to be noted; it indicates a larger dependence upon a resonance component of the total substituent effect than is incorporated in σ_m^+. Further, phenyl (**17**) as a substituent also accelerates the rate of solvolysis. Thus, the results for this very limited set of compounds suggest that the conclusions reached above are also applicable to series B.

Experimental Section[16]

1-(4-Thiazolyl)ethanol (**1**) and **1-(4-Thiazolyl)ethyl chloride** (**2**) have been reported.[11]

1-(2-Methyl-4-thiazolyl)ethanol (**3**).—2-Methyl-4-formylthiazole was prepared by the method of Baganz and Ruger,[17] mp 56–57° (lit.[17] mp 57°), and treated with methylmagnesium bromide to afford alcohol **3** in 78% yield: bp 73–74° (2.0 mm); nmr ($CDCl_3$) δ 1.53 (d, 3, J = 6.3 Hz, $CHCH_3$), 2.65 (s, 3, 2-CH_3), 4.40 (s, 1, OH), 4.95 (q, 1, J = 6.3 Hz, $CHCH_3$), 6.95 (s, 1, 5-H).

Anal. Calcd for C_6H_9NOS: C, 50.32; H, 6.34; N, 9.78; S, 22.39. Found: C, 50.57; H, 6.49; N, 9.59; S, 22.18.

(12) Exemplary are the following: cumyl chlorides, 2.0, 2.28 [Y. Okamoto, T. Inukai, and H. C. Brown, *J. Amer. Chem. Soc.*, **80**, 4972 (1968)]; benzhydryl chlorides, 2.1 [J. F. Norris and J. T. Blake, *ibid.*, **50**, 1808 (1928)]; benzyl tosylates 2.65 [A. Streitwieser, *et al.*, *ibid.*, **92**, 5141 (1970)].

(13) C. G. Swain and E. C. Lupton, Jr., *J. Amer. Chem. Soc.*, **90**, 4328 (1968).

(14) D. S. Noyce and R. W. Nichols, *Tetrahedron Lett.*, 3889 (1972).

(15) M. Charton, *J. Amer. Soc.*, **86**, 2033 (1964).

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

(17) H. Baganz and J. Rüger, *Chem. Ber.*, **101**, 3872 (1968).

1-(2-Methyl-4-thiazolyl)ethyl chloride (4) was prepared from alcohol **3** using phosphorus pentachloride. The chloride was not distilled but characterized by nmr and elemental analysis: nmr ($CDCl_3$) δ 1.92 (d, 3, J = 6.6 Hz, $CHCH_3$), 2.73 (s, 3, 2-CH_3), 5.18 (q, 1, J = 6.6 Hz, $CHCH_3$), 7.17 (s, 1, 5-H).

Anal. Calcd for C_6H_8ClNS: C, 44.58; H, 4.99; Cl, 21.93; N, 8.66. Found: C, 44.70; H, 4.90; Cl, 21.92; N, 8.54.

1-(2-Phenyl-4-thiazolyl)ethanol (6).—2-Phenyl-4-formylthiazole (5) was prepared by the procedure of Baganz and Ruger,[17] mp 48.5–49.0° (lit.[17] mp 52°). Treatment of **5** with methylmagnesium bromide afforded alcohol **6** in 92% yield, separated from small amounts of **5** by chromatography on silica gel: nmr ($CDCl_3$) δ 1.57 (d, 3, J = 6.4 Hz, $CHCH_3$), 4.38 (s, 1, OH), 5.03 (q, 1, J = 6.4 Hz, $CHCH_3$), 7.28 (m, 3, *m*- and *p*-phenyl H), 7.80 (m, 3, 5-H and o-phenyl H).

Anal. Calcd for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82; S, 15.62. Found: C, 64.11; H, 5.28; N, 6.64; S, 15.76.

1-(2-Phenyl-4-thiazolyl)ethyl chloride (7) was prepared from alcohol **6** using phosphorus pentachloride: nmr ($CDCl_3$) δ 1.92 (d, 3, J_{CH,CH_3} = 6.8 Hz, $CHCH_3$), 5.25 (q, 1, J_{CH,CH_3} = 6.8 Hz, $CHCH_3$), 7.17 (s, 1, 5-H), 7.33 (m, 3, *m*- and *p*-phenyl H), 7.87 (m, 2, *o*-phenyl H).

Anal. Calcd for $C_{11}H_{10}ClNS$: C, 59.06; H, 4.50; N, 6.26; S, 14.33. Found: C, 58.97; H, 4.52; N, 6.32; S, 14.34.

4-Formylthiazole Ethylene Acetal (8).—A solution of 4-formylthiazole (4.1 g, 0.0363 mol), ethylene glycol (2.21 ml, 0.04 mol), and *p*-toluenesulfonic acid (0.1 g) in 150 ml of benzene was heated with refluxing. Water was removed with the aid of a Dean-Stark trap. After refluxing for 2.5 hr, the solution was washed with 3 × 30 ml of 2 *N* sodium bicarbonate. The benzene solution was dried ($MgSO_4$) and concentrated to give 3.80 g (67%) of a light yellow oil which was distilled to yield the pure acetal **8**: bp 115–116° (10 mm); ir (neat) 2920, 1470, 1430, 1385, 1325 cm^{-1}; nmr ($CDCl_3$) δ 4.07 (m, 4, OCH_2CH_2O), 6.03 (s, 1, acetal H), 7.45 (d, 1, $J_{2,5}$ = 2.1 Hz, 5-H), 8.88 (d, 1, $J_{2,5}$ = 2.1 Hz, 2-H).

Anal. Calcd for $C_6H_7NO_2S$: C, 45.85; H, 4.49; S, 20.39. Found: C, 45.88; H, 4.67; S, 20.52.

2-Bromo-4-formylthiazole (9).—To a stirred solution of dry ether (500 ml) at −80° under nitrogen atmosphere was added the acetal **8** (16.3 g, 0.104 mol) in 100 ml of ether. Simultaneously from another dropping funnel, *n*-butyllithium (0.115 mol, 71.3 ml in hexane) was added. After the 0.5-hr addition period, the cream-colored suspension was stirred for 45 min before bromine (0.115 mol, 6.32 ml) was added dropwise over a 2-min period. The Dry Ice–acetone bath was removed, and the light yellow solution was stirred for 1 hr before being quenched with 100 ml of water. The layers were separated, and the aqueous phase was extracted with 3 × 50 ml of ether. The combined ether extracts were dried ($MgSO_4$) and concentrated to yield a yellow oil which had spectral properties representative of the desired aldehyde **9** and its ethylene acetal. This oil and 0.1 g of *p*-toluenesulfonic acid were dissolved in 150 ml of dioxane and 100 ml of water and the solution was stirred at 85° for 16 hr. The resulting light brown solution was evaporated to dryness, and the residue was digested in 400 ml of methylene chloride and washed with 3 × 50 ml of water. The organic layer was dried ($MgSO_4$) and concentrated to give 14.0 g (57%) of light brown crystals which were recrystallized from hexane to yield pure **9**: mp 121–123°; nmr ($CDCl_3$) δ 7.10 (s, 1, 5-H), 9.88 (s, 1, CHO).

1-(2-Bromo-4-thiazolyl)ethanol (10).—To a partially dissolved solution of 2-bromo-4-formylthiazole (14.0 g, 0.0729 mol) in 400 ml of dry ether in an ice bath under nitrogen atmosphere was slowly added methylmagnesium bromide (0.071 mol, 24.2 ml of a 2.95 *M* solution in ether). Following the 50-min addition period, the solution was stirred for 30 min before removing the ice bath. After the light tan solution was stirred for an additional 30 min, the solution was quenched with 100 ml of water. The layers were separated and the aqueous phase was extracted with 4 × 50 ml of ether. The aqueous phase was then saturated with ammonium chloride and again extracted with ether (3 × 50 ml). The combined ether were dried ($MgSO_4$) and concentrated to give 12.5 g (83%) of the alcohol **10** and starting material **9** (10% by nmr). The alcohol was purified by elution from a 40-cm column of silica gel with 250 ml of 90% hexane–10% ether: nmr ($CDCl_3$) δ 1.57 (d, 3, J_{CH,CH_3} = 6.6 Hz, $CHCH_3$), 2.90 (s, 1, OH), 4.97 (q, 1, J_{CH,CH_3} = 6.6 Hz, $CHCH_3$), 7.12 (s, 1, 5-H).

1-(2-Bromo-4-thiazolyl)ethyl chloride (11) was prepared from alcohol **10** by treatment with phosphorus pentachloride. Work-up in the usual fashion afforded 79% crude **11** which was further purified by chromatography over silica gel: nmr ($CDCl_3$) δ 1.85 (d, 3, J_{CH,CH_3} = 6.6 Hz, $CHCH_3$), 5.10 (q, 1, J_{CH,CH_3} = 6.6 Hz, $CHCH_3$), 7.22 (s, 1, 5-H).

2-Methylthio-4-formylthiazole (12).—4-Formylthiazole ethylene acetal (**8**, 10.0 g) was metalated with *n*-butyllithium at −80°. After the 20-min addition period, the light tan solution was stirred for an additional 20 min before the rapid addition of methyl disulfide (twofold excess). During the 10-min period, before the Dry Ice–acetone bath was removed, there was no noticable color change in the reaction. The solution was stirred for an additional 45 min before being quenched with 75 ml of water. The resulting clear layers were separated, and the aqueous phase was extracted with 3 × 30 ml of ether. The combined ether extracts were dried ($MgSO_4$) and evaporated to give a yellow oil.[18]

This crude material and *p*-toluenesulfonic acid (0.1 g) were dissolved in 100 ml of dioxane and 100 ml of water and stirred at 75° for 15 hr. The resulting solution was evaporated to dryness, and the tan solid was digested in 300 ml of methylene chloride and washed with 50 ml of water. The organic phase was dried ($MgSO_4$) and concentrated to give 9.5 g (93%) of yellow crystals having excellent spectral properties. The product was purified by recrystallization from hexane to give white flakes of pure aldehyde **12**: mp 74.5–76.0°; nmr ($CDCl_3$) δ 2.75 (s, 3, SCH_3), 8.02 (s, 1, 5-H), 10.0 (s, 1, CHO).

Anal. Calcd for $C_5H_5NOS_2$: C, 37.72; H, 3.16; S, 40.27. Found: C, 37.60; H, 3.25; S, 40.38.

1-(2-Methylthio-4-thiazolyl)ethanol (13).—Treatment of aldehyde **12** with methylmagnesium bromide in ether afforded alcohol **13** in 91% yield, further purified by chromatography on silica gel: nmr ($CDCl_3$) δ 1.53 (d, 3, J_{CH,CH_3} = 6.2 Hz, $CHCH_3$), 2.60 (s, 3, SCH_3), 4.90 (q, 1, J_{CH,CH_3} = 6.2 Hz, $CHCH_3$), 6.97 (s, 1, 5-H).

Anal. Calcd for $C_6H_9NOS_2$: C, 41.12; H, 5.18; S, 36.59. Found: C, 40.90; H, 5.14; S, 36.78.

1-(2-Methylthio-4-thiazolyl)ethyl Chloride (14).—Treatment of alcohol **13** with phosphorus pentachloride in methylene chloride gave chloride **14** in 87% yield: mp 104–105°; nmr ($CDCl_3$) δ 1.85 (d, 3, J = 6.6 Hz, $CHCH_3$), 2.67 (s, 3, 2-SCH_3), 5.13 (q, 1, J = 6.6 Hz, $CHCH_3$), 7.08 (s, 1, 5-H).

Anal. Calcd for $C_6H_8ClNS_2$: C, 37.20; H, 4.16; N, 7.23; S, 33.10. Found: C, 37.22; H, 4.32; N, 7.14; S, 33.22.

1-(4-Methyl-2-thiazolyl)ethyl Chloride (15).—To a stirred solution of 1-(4-methyl-2-thiazolyl)ethanol[19] (5.45 g, 0.038 mol) in 60 ml of carbon tetrachloride at room temperature under nitrogen, phosphorus pentachloride (7.94 g, 0.038 mol) was slowly added. After the initial reaction subsided, the light yellow solution was stirred for 2 hr. Ether (100 ml) was added, and the mixture was stirred with a slurry of aqueous sodium bicarbonate (5 ml). The organic layer was separated, dried ($MgSO_4$), and distilled to give 3.29 g (54%) of pure chloride **15**: bp 71° (4 mm); nmr ($CDCl_3$) δ 1.80 (d, 3, J = 7.0 Hz, $CHCH_3$), 2.28 (d, 3, $J_{5,4-CH_3}$ = 1.0 Hz, 4-CH_3), 5.18 (q, 1, J = 7.0 Hz, $CHCH_3$), 6.75 (q, 1, $J_{5,4-CH_3}$ = 1.0 Hz, 5-H).

Anal. Calcd for C_6H_8ClNS: C, 44.58; H, 4.99; Cl, 21.93; N, 8.66; S, 19.84. Found: C, 44.61; H, 5.14; Cl, 22.12; N, 8.59; S, 19.90.

1-4-Phenyl-2-thiazolyl)ethyl Chloride (17).—1-(4-Phenyl-2-thiazolyl)ethanol (**16**)[20] was converted to chloride **17**, by treatment of **16** with phosphorus pentachloride in methylene chloride: yield 84%; mp 36.5–37.5°; nmr ($CDCl_3$) δ 1.95 (d, 3, J = 6.5 Hz, $CHCH_3$), 5.37 (q, 1, J = 6.5 Hz, $CHCH_3$), 7.35 (m, 3, *m*- and *p*-phenyl H), 7.37 (s, 1, 5-H), 7.85 (m, 2, *o*-phenyl H).

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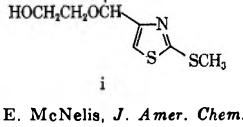
(18) This oil had spectral properties indicative of the mixed thioacetal i: nmr ($CDCl_3$) δ 2.38 (s, 3, SCH_3), 2.63 (s, 3, 2-SCH_3), 4.03 (s, 5, OCH_2CH_2OH), 5.90 (s, 1, acetal H), 7.23 (s, 1, 5-H).



i

(19) R. Breslow and E. McNelis, *J. Amer. Chem. Soc.*, **81**, 3080 (1959); improved yields (76%) were obtained using an excess of acetaldehyde.

(20) 1-(4-Phenyl-2-thiazolyl)ethanol is conveniently prepared by metalation of 4-phenylthiazole with butyllithium followed by treatment with acetaldehyde: yield 71%; mp 73–74° (lit. mp 76°) [J. Folin and T. B. Johnson, *J. Amer. Chem. Soc.*, **53**, 1473 (1931)].

Anal. Calcd for $C_{11}H_{10}ClNS$: C, 59.05; H, 4.51; Cl, 15.85; N, 6.26. Found: C, 58.97; H, 4.34; Cl, 16.05; N, 6.37.

1-(4,5-Dimethyl-2-thiazolyl)ethanol (18).—Metalation of 4,5-dimethylthiazole with *n*-butyllithium at −80° was followed by addition of a threefold excess of acetaldehyde. Isolation in the usual fashion afforded **18** in 71% yield: bp 186–188° (150 mm) [lit.[21] bp 120–123° (10 mm)]; mp 53–55°; nmr ($CDCl_3$) δ 1.52 (d, 3, J = 6.5 Hz, $CHCH_3$), 2.22 (s, 3, 4-CH_3), 2.27 (s, 3, 5-CH_3), 5.00 (q, 1, J = 6.5 Hz, $CHCH_3$), 5.70 (s, 1, OH).

Anal. Calcd for $C_7H_{11}NOS$: C, 53.47; H, 7.05; N, 8.91. Found: C, 53.29; H, 7.02; N, 8.85.

1-(4,5-Dimethyl-2-thiazolyl)ethyl chloride (19) was prepared from **18** using phosphorus pentachloride: bp 151–157° (44 mm); nmr ($CDCl_3$) δ 1.88 (d, 3, J = 6.5 Hz, $CHCH_3$), 2.30 (6, 4-CH_3 and 5-CH_3), 5.23 (q, 1, J = 6.5 Hz, $CHCH_3$).

Anal. Calcd for $C_7H_{10}ClNS$: C, 47.86; H, 5.74; Cl, 20.18; N, 7.94; S, 18.25. Found: C, 47.98; H, 5.97; Cl, 20.32; N, 8.08; S, 18.10.

Kinetic procedures have been described previously.[5]

Registry No.—**3**, 41029-77-0; **4**, 41029-78-1; **5**, 20949-81-9; **6**, 41029-80-5; **7**, 41029-81-6; **8**, 41029-82-7; **9**, 5198-80-1; **10**, 41029-84-9; **11**, 41029-85-0; **12**, 41029-86-1; **13**, 41029-87-2; **14**, 41029-88-3; **15**, 41029-89-4; **16**, 41029-90-7; **17**, 41029-91-8; **18**, 7531-72-8; **19**, 41029-93-0; 2-methyl-4-formylthiazole, 20949-84-2; 4-formylthiazole, 3364-80-5; ethylene glycol, 107-21-1; *p*-toluenesulfonic acid, 104-15-4; 1-(4-methyl-2-thiazolyl)ethanol, 7586-99-4; 4,5-dimethylthiazole, 3581-91-7; *n*-butyllithium, 109-72-8; thioacetal i,[18] 41029-97-4.

(21) J. Okimaya, *Nippon Kagaku Zasshi*, **87**, 594 (1966); *Chem. Abstr.*, **65**, 15362*C* (1966).

Syntheses with N-Protected 2-Lithioindoles

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Received April 18, 1973

A series of potential N-protecting groups which would permit syntheses *via* N-protected 2-lithioindoles has been investigated. These include the methoxymethyl, benzyloxymethyl, benzyl, benzenesulfonyl, trimethylsilyl, and *tert*-butyldimethylsilyl groups. The methoxymethyl and benzenesulfonyl derivatives of indole have been shown to be satisfactorily lithiated and to give addition reactions with typical carbonyl and cyano compounds. The benzenesulfonyl group has a major advantage over the methoxymethyl group for subsequent removal. A number of new 2-acylindoles and 2-indolylcarbinols prepared by these reactions are described. Certain competing reactions leading to by-products have also been detected and are described.

It was demonstrated some years ago[1] that 1-methylindole could be efficiently converted to the 2-lithio derivative by lithiation with *n*-butyllithium. Although there has subsequently been some use of this reaction in synthetic work,[2-4] the utility of this particular lithium derivative is restricted to *N*-alkylindoles, since there is no suitable means for subsequently dealkylating the reaction products. Since 2-lithioindoles could provide a quite general synthetic route to 2-substituted indoles, we have undertaken efforts to develop a procedure for lithiation of indoles substituted by a group which could subsequently be removed under relatively mild conditions. We report here our examination of the methoxymethyl, benzyloxymethyl, benzyl, benzenesulfonyl, trimethylsilyl, and *tert*-butyldimethylsilyl groups for this purpose.[5]

Synthesis of N-Protected Indoles.—The data of Cardillo, *et al.*, indicate that syntheses of 1-alkylated indole could be expected to proceed very efficiently in dipolar aprotic solvents.[6] We found it convenient to effect the alkylations in dimethyl sulfoxide. The sodium salt of dimethyl sulfoxide was generated in the usual way,[7] and indole was then added, forming the sodium salt. The alkylating agent was then added. The yields of **1a**, **1b**, **1c**, and **1d** by this procedure were excellent.[8] Others[9] have recommended hexamethylphosphoramide as a solvent or cosolvent for indole alkylations. The *N*-silyl compounds **1e** and **1f** were prepared in tetrahydrofuran solution because of the reactivity of the silyl chlorides toward dimethyl sulfoxide.

Lithiation.—The extent of lithiation was determined by treating a solution of the N-substituted indole in ether, THF, or tetramethylethylenediamine (TMEDA) with *tert*-butyllithium, quenching with D_2O, and determination of the extent and location of deuterium incorporation by analysis of the mass spectrum. Details of the mass spectral analysis are given in the Experimental Section. The results are summarized in Table I. Of the systems studied only **1a** and **1d** gave relatively clean-cut 2 deuteration. Only these two systems were, therefore, subjected to study with respect to use as a protecting group in subsequent synthetic transformations.

Our studies have given some insight into the course of the reaction of the other four systems with *tert*-butyllithium, which we will summarize here briefly. Not surprisingly, the benzyl compound **1c** is lithiated competitively at the benzyl methylene group. The mass spectrum of recovered **1c** indicates 55% incorporation of D at that position with only 15% lithiation at

(1) D. A. Shirley and P. A. Roussel, *J. Amer. Chem. Soc.*, **75**, 375 (1953).

(2) F. E. Ziegler and E. B. Spitzner, *J. Amer. Chem. Soc.*, **92**, 3492 (1970).

(3) J. Kebrle and K. Hoffmann, *Gazz. Chim. Ital.*, **93**, 238 (1963).

(4) J. Kebrle, A. Rossi, and K. Hoffmann, *Helv. Chim. Acta*, **42**, 907 (1959).

(5) Some previous work using these or similar groups on indole or related heterocycles follows. (a) Methoxymethyl: M. H. Karger and Y. Mazur, *J. Amer. Chem. Soc.*, **91**, 5663 (1969). (b) Benzyloxymethyl: H. J. Anderson and J. K. Groves, *Tetrahedron Lett.*, 3165 (1971). (c) Arenesulfonyl: R. E. Bowman, D. D. Evans, and P. J. Islip, *Chem. Ind. (London)*, 33 (1971); R. E. Bowman, D. D. Evans, J. Guyett, H. Nagy, J. Weale, D. J. Weyell, and A. C. White, *J. Chem. Soc., Perkin Trans. 1*, 1926 (1972); W. A. Remers, R. H. Roth, G. J. Gibs, and M. J. Weiss, *J. Org. Chem.*, **36**, 1232 (1971); R. E. Bowman, D. D. Evans, J. Guyett, H. Nagy, J. Weale, and D. J. Weyell, *J. Chem. Soc., Perkin Trans. 1*, 438 (1973). (d) Trialkylsilyl (previous preparation of N-silated indole has been recorded but we are not aware of examples where the group has been employed specifically as a protecting group): R. Fessenden and D. F. Crowe, *J. Org. Chem.*, **26**, 4638 (1961).

(6) B. Cardillo, G. Casnati, A. Pochini, and A. Ricca, *Tetrahedron*, **23**, 3771 (1967).

(7) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 866 (1962); **87**, 1353 (1965).

(8) Excellent results in dimethyl sulfoxide using potassium hydroxide as the base have been reported recently: H. Heaney and S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, 498 (1973).

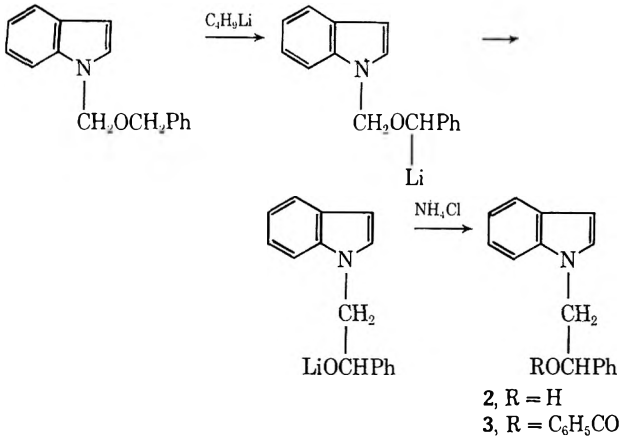
(9) (a) G. M. Rubottom and J. C. Chabala, *Synthesis*, 566 (1972); (b) M. G. Reinecke, J. F. Sebastian, H. W. Johnson, and C. Pyun, *J. Org. Chem.*, **37**, 3066 (1972).

TABLE I

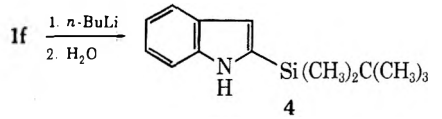
LITHIATION OF 1-SUBSTITUTED INDOLE BY *tert*-BUTYLLITHIUM

Compd	1 substituent	Solvent for lithiation	Yield of recovered indole, %	Total D incorporation, %	D incorporation at C-2, %
1a	CH_3OCH_2	Et_2O	77	95	95
1b	$PhCH_2OCH_2$	Et_2O	35	40	30
1c	$PhCH_2$	THF	90	70	15
1d	$PhSO_2$	THF	90	97	86
		TMEDA	85	90	88
1e	$(CH_3)_3Si$	TMEDA	0		
1f	$(CH_3)_3C(CH_3)_2Si$	THF	85	0	0
		TMEDA	60	0	0

the C-2 position of the ring. The nitrogen–silicon bond in 1-trimethylsilylindole is cleaved by *tert*-butyllithium and only unsubstituted indole is found after lithiation. The situations with **1b** and **1f** are not quite so straightforward. The problem with **1b** is a competing lithiation at the benzyl group followed by Wittig rearrangement.[10] The rearranged alcohol **2** was isolated in ~65% yield after lithiation and D_2O quench. The derived benzoate ester **3** was isolated after treatment of the lithiation mixture with benzoyl chloride.

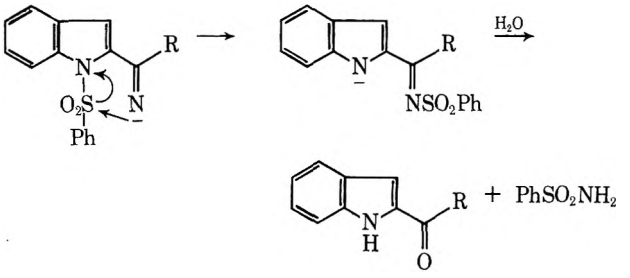


The very bulky silyl substituent in **1f** exerts a strong steric influence and we did not observe any lithiation on reaction with *tert*-butyllithium. With *n*-butyllithium reaction occurred but a rearrangement of the 2-lithio derivative ensued and after deuteration the product was found to be 2-[dimethyl-(1,1-dimethylethyl)silyl]indole (**4**). The rearrangement is an example of anionic rearrangement of silane derivatives which have been studied extensively by West and coworkers.[11]

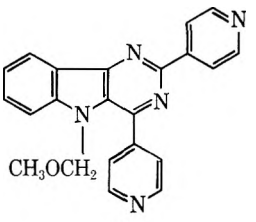


4

Synthetic Transformations of Protected 2-Lithioindoles.—Reactions of the lithio derivatives of **1a** (2-LiMMI) and **1d** (2-LiBSI) were run with typical substrates used in organometallic synthetic procedures including aldehydes, ketones, acid chlorides, esters, and nitriles. In most instances these reactions proceeded to give the expected product in moderate yields. In a few cases efforts were made to optimize individual reaction conditions. In these cases some improvement in yields was noted but yields seldom exceeded 70%, indicating that some, as yet unidentified, competitive reactions are occurring. The data are summarized in Table II and the spectral properties of the products are given in the Experimental Section. This data normally was sufficient to corroborate the identity of the products. In other cases the products were known compounds and the physical constants were in satisfactory agreement with literature data. One point of interest is the fact that the benzenesulfonyl substituent was cleaved during the reaction or work-up in the case of reactions with esters and nitriles. The 2-acyl substituent, which increases the stability of the indolyl anion, may be at least partially responsible for this facile removal of protecting group. In reactions involving nitriles, benzenesulfonamide was isolated in several instances. Its formation indicates that transfer of the benzenesulfonyl substituent to the imine nitrogen may precede hydrolysis of the intermediate imine.



Identifiable by-products were noted in only a few of the reactions. In the reaction of 2-LiMMI with 4-cyanopyridine, a yellow solid, **26**, mp 251.5–252.5°, having the formula $C_{22}H_{17}N_5O$ was isolated in up to 84% yield. The mass spectrum consisted of only a few ions, suggesting a highly aromatic structure for this material. The available data is in accord with assigning the structure 5-methoxymethyl-2,4-di(4-pyridyl)pyrimido[5,6-*b*]indole to this material. It is formally derived from a two-electron oxidation of a 2:1 adduct of 4-cyanopyridine with 2-LiMMI. Its formation may involve aromatization by elimination of LiH.



26

(10) H. E. Zimmerman, "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1963, pp 372–377; D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, pp 230–233; U. Schöllkopf, *Angew. Chem., Int. Ed. Engl.*, **9**, 763 (1970).

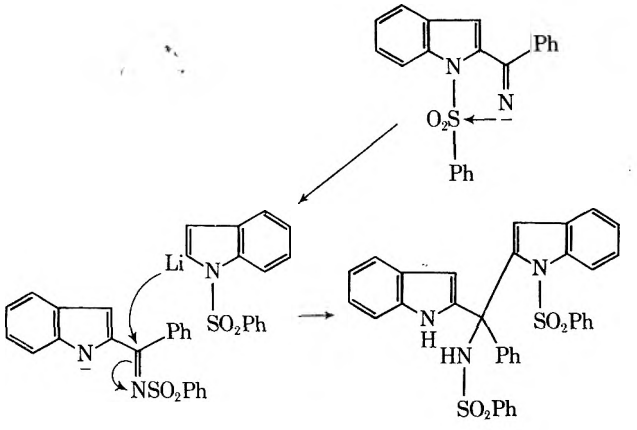
(11) A. Wright, D. Ling, P. Boudjouk, and R. West, *J. Amer. Chem. Soc.*, **94**, 4784 (1972), and preceding papers.

TABLE II

REACTIONS OF 1-PROTECTED 2-LITHIOINDOLES WITH TYPICAL FUNCTIONAL GROUPS

Reactant	Reaction product	Isolated yield, %
	A. 2-LiMMI	
Benzaldehyde	(1-Methoxymethylindol-2-yl)phenylmethanol (5)	40
Carbon dioxide	1-Methoxymethyl-2-indolecarboxylic acid (6)	80
N-Methylformanilide	1-Methoxymethyl-2-indolecarboxaldehyde (7)	46
Benzonitrile	1-Methoxymethyl-2-indolyl phenyl ketone (8)	84
4-Methoxybenzonitrile	1-Methoxymethyl-2-indolyl 4-methoxyphenyl ketone (9)	70
2-Cyanopyridine	1-Methoxymethyl-2-indolyl 2-pyridyl ketone (10)	56
4-Cyanopyridine	1-Methoxymethyl-2-indolyl 4-pyridyl ketone (11)	56
	B. 2-LiBSI	
Benzaldehyde	(1-Benzenesulfonylindol-2-yl)phenylmethanol (12)	55
4-Methoxybenzaldehyde	(1-Benzenesulfonylindol-2-yl)(4-methoxyphenyl)methanol (13)	65
2-Pyridinecarboxaldehyde	(1-Benzenesulfonylindol-2-yl)-2-pyridylmethanol (14)	32
Acetophenone	1-(1-Benzenesulfonylindol-2-yl)-1-phenylethanol (15)	64
4-Methoxyacetophenone	1-(Benzenesulfonylindol-2-yl)-1-(4-methoxyphenyl)ethanol (16)	35
4-Acetylpyridine	1-(1-Benzenesulfonylindol-2-yl)-1-(4-pyridyl)ethanol (17)	35
Benzoyl chloride	1-Benzenesulfonyl-2-indolyl phenyl ketone (18)	65
Nicotinyl chloride	1-Benzenesulfonyl-2-indolyl 3-pyridyl ketone (19)	60
Ethyl chloroformate	Ethyl 1-benzenesulfonylindole-2-carboxylate (20)	75
Carbon dioxide	1-Benzenesulfonylindole-2-carboxylic acid (21)	63
Ethyl benzoate	2-Indolyl phenyl ketone (22)	26
Ethyl isonicotinate	2-Indolyl 4-pyridyl ketone (23)	31
Ethyl nicotinate	2-Indolyl 3-pyridyl ketone (24)	22
Benzonitrile	2-Indolyl phenyl ketone (22)	30
2-Cyanopyridine	2-Indolyl 2-pyridyl ketone (25)	36
4-Cyanopyridine	2-Indolyl 4-pyridyl ketone (23)	26

Several of the reactions of aromatic nitriles, especially benzonitrile, with 2-LiBSI gave a solid which had the composition corresponding to addition of two benzenesulfonylindole moieties to the nitrile. Structural investigation of the product from benzonitrile indicated that the compound is **27**, perhaps formed by the mechanism shown from the 1:1 adduct.

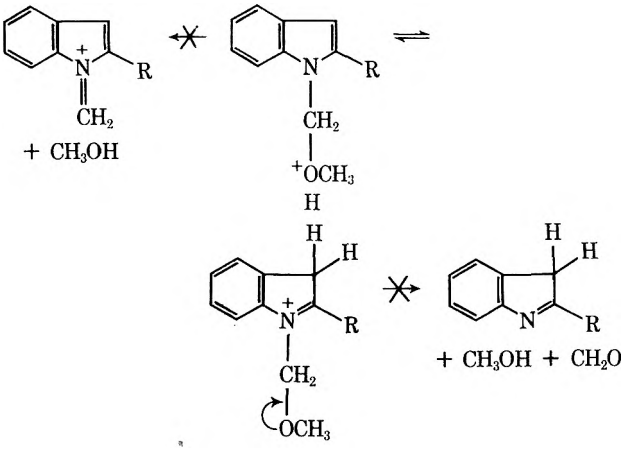


27

The mass spectrum of the compound near 200° is essentially identical with that of benzenesulfonamide. This fact is compatible with the rearrangement of the benzenesulfonyl group to a nitrogen atom derived from the nitrile. Peaks corresponding to elimination of benzenesulfonamide are not prominent in the mass spectra of compounds containing the benzenesulfonyl group as a 1 substituent on the indole ring.

In reactions of 2-LiBSI with ethyl nicotinate a pale yellow solid, mp 182–184°, having the formula $C_{22}H_{16}N_2O_2S$ was isolated in 11% yield. The mass spectrum showed a single major fragmentation with loss of the benzenesulfonyl moiety (*m/e* 141) and the nmr spectrum is in good agreement with the structure 1-benzenesulfonyl-2,2′-biindole (**28**). Hydrolysis of this compound with methanolic base gave a solid with spectral properties in accord with those expected for 2,2′-biindole (**29**), mp 301–305° (lit.[12] mp 308–310°).

Substituent Cleavage.—The methoxymethyl substituent was completely resistent to hydrolytic cleavage in acidic aqueous media. This result, which is surprising if the NCH_2OCH_3 is considered a typical carbinolamine grouping, reflects the delocalized nature of the electron pair at nitrogen. A possible alternative hydrolysis



mechanism *via* elimination of the 3*H*-indole tautomer is also evidently energetically demanding. The substituent could be cleaved in acetic anhydride utilizing lithium bromide and boron trifluoride as coreactants, but these vigorous conditions were restricted to 2-acylindoles since 2-indolylcarbinols are too sensitive to survive such vigorous conditions.[13]

The benzenesulfonyl group can be removed by relatively mild alkaline hydrolysis.[5c,14] These conditions

(12) S. A. Faseeh and J. Harley-Mason, *J. Chem. Soc.*, 4141 (1957).

(13) F. E. Ziegler, E. B. Spitzner, and C. K. Wilkins, *J. Org. Chem.*, **36**, 1759 (1971).

(14) C. D. Jones, *J. Org. Chem.*, **37**, 3624 (1972).

were successfully tested with compounds **12**, **13**, **18**, and **24** and the substituent cleavage was found to occur in excellent yield (80–95%).

These results indicate that the benzenesulfonyl group meets the necessary requirements as an N-protecting group in syntheses *via* 2-lithioindoles. It can be conveniently introduced and removed and does not usually interfere with either lithiation or subsequent reactions of the intermediate.

Experimental Section

General.—All reactions involving indole derivatives were run under nitrogen. All lithium compounds were transferred by syringe. Unless otherwise indicated the infrared bands quoted are for KBr pellets.

Preparation of N-Substituted Indoles.—A general procedure was applicable to **1a**, **1b**, **1c**, and **1d**. Sodium methylsulfinylmethide was prepared from sodium hydride and dimethyl sulfoxide as described by Corey and Chaykovsky.[7] The solution was cooled with an ice bath and 1 equiv of indole in ether solution was added dropwise, followed by stirring for 0.5 hr while warming to room temperature. The suspension which resulted was cooled to 0° and a solution of the appropriate chloride (1.1 equiv) was added dropwise with stirring. The reaction mixture was allowed to stir at room temperature for 0.5 hr and then a small amount of water was added. The reaction mixture was then poured into excess water, extracted thoroughly with ether, and evaporated to give the crude product. Specific purification procedures are described below.

1-Methoxymethylindole (1a).—The crude product from alkylation of indole (30 mmol) by methoxymethyl chloride was distilled to give a colorless oil (4.3 g, 90%): bp 69–71° (0.1 mm); nmr ($CDCl_3$) δ 3.15 (s, 3), 5.32 (s, 2), 6.45 (d, 1, J = 4 Hz), and 7.0–7.7 (m, 5).

Anal. Calcd for $C_{10}H_{11}NO$: C, 74.53; H, 6.83; N, 8.69. Found: C, 74.75; H, 6.90; N, 8.63.

1-Benzyloxymethylindole (1b).—The crude product from alkylation of indole (30 mmol) with benzyloxymethyl chloride[15] was purified by chromatography on Florisil using 2:1 hexane–benzene to elute **1b** as a pale yellow oil (8.5 g, 80%). Small quantities could be further purified by vacuum distillation: bp 156–158° (1.0 mm); nmr ($CDCl_3$) δ 4.3 (s, 2), 5.4 (s, 2), 6.48 (d, 1), 7.0–7.7 (m, 10).

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.73; H, 6.49; N, 5.84.

1-Benzylindole (1c).—Vacuum distillation of the crude product from a 50-mmol run gave **1c** (9.18 g, 89%), bp 141–143° (0.3 mm) [lit.[16] bp 172° (2 mm)].

1-Benzenesulfonylindole (1d).—The crude product from a 0.30-mol run was obtained as a pale orange-yellow oil which solidified on trituration with 2:1 hexane–ether. Recrystallization from methylene chloride–hexane using charcoal gave **1d** as white needles (70 g, 92%): mp 77.5–79°; nmr ($CDCl_3$) δ 6.53 (d, 1, J = 4 Hz), 7.0–8.1 (m, 10); $\lambda_{max}^{95\%\ EtOH}$ 252 nm (log ϵ 4.17), 275 (sh, 3.60), 285 (sh, 3.51), 292 (sh, 3.48).

Anal. Calcd for $C_{14}H_{11}NO_2S$: C, 65.36; H, 4.31; N, 5.44; S, 12.44. Found: C, 65.34; H, 4.33; N, 5.45; S, 12.55.

1-Trimethylsilylindole[17] **(1e).**—A solution of indole (2.34 g, 20 mmol) in THF was cooled to −12°. *n*-Butyllithium (9.5 ml of 2.1 *M* solution) was added and the reaction mixture was allowed to warm to room temperature with stirring. The solution was again cooled to −10° and a solution of trimethylchlorosilane (3.25 ml) in THF was added dropwise. The reaction mixture was stirred overnight at room temperature. After removal of a white precipitate by filtration, the solvent was evaporated and the residue was distilled to give **1e** (2.2 g, 60%) as a clear liquid: bp 82–84° (0.4 mm); ν_{NH} none; nmr (CCl_4) δ 0.56 (s, 9), 6.47 (d, J = 3 Hz, 1), and 6.9–7.6 (m, 5).

1-[Dimethyl(1,1-dimethylethyl)silyl]indole (1f).—The procedure described for **1e** using *tert*-butyldimethylchlorosilane[18] provided **1f** (3.5 g, 86%) as a liquid, bp 116–117° (1.0 mm), which solidified on standing: mp 38–39°; ν_{NH} none; nmr (CCl_4) δ 0.6 (s, 6), 0.95 (s, 9), 6.45 (d, 1, J = 4 Hz), and 6.85–7.6 (m, 5).

Anal. Calcd for $C_{14}H_{21}NSi$: C, 72.66; H, 9.15; N, 6.05. Found: C, 72.68; H, 9.21; N, 6.06.

2-Lithio-1-methoxymethylindole (2-LiMMI).—A solution of 2.3 *M* *tert*-butyllithium in hexane (12 mmol) was cooled to 0° and a solution of **1a** (1.61 g, 10 mmol) in ether was added. The orange solution was allowed to stir at room temperature for 30 min–1 hr and then used as outlined for the individual reactions.

1-Benzenesulfonyl-2-lithioindole (2-LiBSI).—A solution of 10 mmol of **1d** in ether, THF, or TMEDA was cooled to −12°. A pentane solution of *tert*-butyllithium (11–12 mmol) was added from a syringe at a moderate rate. The resulting deep red-orange solution was allowed to warm to room temperature over 15–20 min. Such solutions were used for the individual reactions described below.

Attempted Lithiation of 1-Benzyloxymethylindole (1b).—A solution of **1b** (1.185 g, 5 mmol) in THF was cooled in an ice–salt bath and 14.3 ml of 1.4 *M* *tert*-butyllithium was added. After 10 min D_2O (0.2 ml) was added and the solution was stirred for 15 min. An ether solution of the product was dried and evaporated. Chromatography of the product on Florisil gave 0.77 g (65%) of **2** having ir and nmr spectral properties similar to those of pure **2**. Further purification by preparative layer chromatography gave pure **2** which was recrystallized from chloroform–hexane: mp 83–85°; ν_{OH} 3650–3200 cm^{-1}; nmr (benzene-d_6) δ 1.85 (broad singlet), 3.75 (d, 2, J = 6 Hz), 4.4 (broad t, 1, J = 6 Hz), 6.35 (d, 1, J = 3 Hz), 6.68 (d, 1, J = 3 Hz), 6.9–7.7 (multiplet with prominent singlet at 7.0, 9).

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.82; H, 6.39; N, 5.95.

Benzoylation in pyridine gave the *O*-benzoyl derivative **3**: ν_{OH} none; ν_{CO} 1730 cm^{-1}; nmr ($CDCl_3$) δ 4.4–4.6 (AB portion of an ABX system with δ_a 4.60, δ_b 4.44, J_{ax} = 7, J_{bx} = 5, and J_{ab} = 14 Hz), 6.1–6.4 (m, 2, consists of t, 6.25, J = 6 Hz, and d, 6.35, J = 3.5 Hz), 6.82 (d, 1, J = 3.5 Hz), 6.9–7.7 (multiplet with prominent singlet at δ 7.25, 12), and 7.85–8.1 (m, 2). This compound was also isolated when the lithiation solution (prior to hydrolysis) was treated with benzoyl chloride.

2-[Dimethyl(1,1-dimethylethyl)silyl]indole (4).—A solution of **1f** (0.93 g, 4.0 mmol) in TMEDA was treated with 2.2 *M* *n*-butyllithium (1.85 ml, 4.07 mmol) and stirred at 100° for 2 hr. The reaction mixture was diluted and the product was isolated by extraction. The ether extract was washed with 1% hydrochloric acid, dried, and evaporated. Tlc showed the product to be a mixture of **1f** and **4**, mainly the latter. Pure **4** was isolated by preparative layer chromatography: mp 28–30°; ν_{NH} 3440 cm^{-1}; nmr (CCl_4) δ 0.3 (s, 6), 0.95 (s, 9), 6.5 (d, 1, J = 3 Hz), 6.8–7.8 (m, 5).

Anal. Calcd for $C_{14}H_{21}NSi$: C, 72.66; H, 9.15; N, 6.05. Found: C, 72.72; H, 9.23; N, 6.10.

Determination of Extent of Lithiation.—A solution of 5 mmol of the 1-substituted indole in 10 ml of anhydrous solvent (ether, THF, or TMEDA as noted in Table I) was cooled in an ice–acetone bath. To this solution was added 5.1 mmol of *tert*-butyllithium as a 1–2 *M* solution in pentane. The cooling bath was removed and the solution was warmed to room temperature during 15–20 min. Deuterium oxide (10 mmol) was added *via* syringe and the solution was stirred for 10 min. Ether and THF solutions were diluted with additional ether, dried over potassium carbonate, and evaporated. Reactions run in TMEDA were poured into a tenfold excess of water and extracted with ether. The combined ether extracts were washed with dilute hydrochloric acid, dried, and evaporated. In either case the crude product obtained by solvent evaporation was purified by preparative layer chromatography on silica gel and then analyzed for deuterium content by mass spectrometry. Total deuterium incorporation was derived from the parent peak region and the location was determined by measuring per cent deuteration of one or more appropriate fragment ions, using the method of calculation described by Biemann.[19] Good internal consistency of the results was found, indicating that no serious complications are arising from hydrogen migrations in the mass spectrometer.

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(1-Methoxymethylindol-2-yl)phenylmethanol (5).—To a solution of 2-LiMMI (20 mmol) in TMEDA was added dropwise at room temperature a THF solution of benzaldehyde (20 mmol) and the resulting solution was stirred at room temperature for 0.5 hr. The reaction mixture was poured into water and extracted with ether. The extract was washed with 1% hydrochloric acid, dried, and evaporated. Chromatography on silica gel gave 5 (2.15 g, 40%) as an oily solid. After distillation (195–196°, 3 mm) the oil was recrystallized from ether–hexane: mp 69–71°; nmr ($CDCl_3$) δ 3.1 (s, 3), 5.25 (s, 2), 5.92 (broad s, 1), 6.18 (s, 1), 6.95–7.6 (m, 10).

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.33; H, 6.48; N, 5.19.

1-Methoxymethylindole-2-carboxylic Acid (6).—A solution of 2-LiMMI (15 mmol) was poured into an ether–Dry Ice slurry. After evaporation of the Dry Ice and solvent, the residue was refluxed for 15 min with an aqueous oxalic acid solution and then extracted with methylene chloride. The product was purified by elution from silicic acid by 1:1.5 ether–benzene (2.5 g, 80%): mp 153–154° after recrystallization from ether–hexane; nmr (DMSO-d_6) δ 3.20 (s, 3), 6.00 (s, 2), 7.07–7.8 (m, 5).

Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.42; H, 5.52; N, 6.90.

1-Methoxymethylindole-2-carboxaldehyde (7).—A solution of 2-LiMMI (10 mmol) was allowed to warm to room temperature and treated dropwise with an ether solution of *N*-methylformanilide (1.35 g, 10 mmol). The resulting suspension was refluxed for 3 hr, cooled, and hydrolyzed with 5% hydrochloric acid. The product was isolated by extraction with ether and purified by elution from Florisil with 1:1 hexane–benzene to give 7 (0.9 g, 46%) as an oil: bp 110–112° (0.1 mm); ν_{CO} 1680 cm^{-1} (neat); nmr ($CDCl_3$) δ 3.22 (s, 3), 5.86 (s, 2), 7.0–7.8 (m, 6), and 9.8 (s, 1).

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.59; H, 5.95; N, 7.20.

1-Methoxymethyl-2-indolyl Phenyl Ketone (8).—An ether solution of benzonitrile (1.03 g, 10 mmol) was added dropwise at 0° to 2-LiMMI (10 mmol) and then stirred overnight at room temperature. After hydrolysis with aqueous ammonium chloride, the product was isolated by extraction with ether. Pure 8 was eluted from silicic acid by 1:9 benzene–hexane (2.24 g, 84%) and recrystallized from hexane: mp 56–57.5°; ν_{CO} 1640 cm^{-1}; nmr ($CDCl_3$) δ 3.30 (s, 3), 5.98 (s, 2), and 7.0–8.0 (m, 10).

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Fund: C, 76.88; H, 5.72; N, 5.32.

A minor amount of 2,4,6-triphenyl-*s*-triazine, mp 234.5–235.5° (lit.[20] mp 234°), was identified as a by-product of this reaction.

1-Methoxymethyl-2-indolyl 4-Methoxyphenyl Ketone (9).—An ether solution of 4-methoxybenzonitrile (1.99 g, 15 mmol) was added dropwise at 0° to a solution of 2-LiMMI (15 mmol). The solution was then stirred for 1 hr at room temperature. After hydrolysis and extraction with ether, 9 was purified by elution from alumina with 1:5 ether–hexane (3.16 g, 70%) and recrystallized from chloroform–hexane: mp 97–98.5°; ν_{CO} 1640 cm^{-1}; nmr ($CDCl_3$) δ 3.28 (s, 3), 3.80 (s, 3), 5.90 (s, 2), 6.93 (d, 2, J = 8 Hz), 7.0–7.8 (m, 5), and 7.92 (d, 2, J = 8 Hz).

Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 72.78; H, 5.85; N, 4.81.

1-Methoxymethyl-2-indolyl 2-Pyridyl Ketone (10).—A solution of 2-cyanopyridine (1.04 g, 10 mmol) was added to 2-LiMMI (10 mmol) and stirred for 1 hr at room temperature. After hydrolysis with ammonium chloride, the product was isolated by extraction with ether and purified by elution from silicic acid with 1:9 ether–benzene (1.5 g, 56%): mp 92–93.5° after recrystallization from benzene–hexane; ν_{CO} 1645 cm^{-1}; nmr ($CDCl_3$) δ 3.35 (s, 3), 6.06 (s, 2), 7.0–8.15 (m, 8), and 8.7 (d, 1, J = 5 Hz).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.04; H, 5.33; N, 10.47.

1-Methoxymethyl-2-indolyl 4-Pyridyl Ketone (11).—A solution of 4-cyanopyridine (1.04 g, 10 mmol) in ether was added slowly to an ice-cooled solution of 2-LiMMI (10 mmol). The resulting suspension was stirred for 1 hr at room temperature and then hydrolyzed with ammonium chloride solution. The product mixture was extracted with ether and separated by chromatography on silicic acid. Ether–benzene (1:9) eluted 11 (1.5 g, 56%): mp 90–91° after recrystallization from hexane; ν_{CO} 1645 cm^{-1}; nmr ($CDCl_3$) δ 3.35 (s, 3), 6.0 (s, 2) 7.0–7.5 (m, 7), and 8.75 (d, 2, J = 5 Hz).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.03; H, 5.30; N, 10.51.

This was followed by variable amounts of up to 10% of 5-methoxymethyl-2,4-bis(4-pyridyl)pyrimido[5,6-*b*]indole (26): mp 251.5–252.5° after recrystallization from chloroform–hexane; $\lambda_{max}^{95\%\ EtOH}$ 237 nm (sh, log ϵ 4.25), 249 (4.38), 255 (4.39), 287 (sh, 3.85), 388 (3.89); mass spectrum *m/e* (rel intensity) 367 (49), 352 (73), 337 (47), 324 (100), 45 (58).

Anal. Calcd for $C_{22}H_{17}N_5O$: C, 71.92; H, 4.66; N, 19.06. Found: C, 71.69; H, 4.73; N, 19.01.

When the reaction was run in THF, 26 was the major product (84% yield).

1-(1-Benzenesulfonylindol-2-yl)phenylmethanol (12).—A solution of benzaldehyde (1.15 g, 10.1 mmol) in TMEDA was added dropwise to 2-LiBSI (10 mmol) in TMEDA at −10°. The solution was stirred overnight at room temperature. After isolation by extraction the product was purified by elution from a silica gel column with 5% ether in benzene. The compound solidified on trituration with ether (1.97 g, 55%) and was recrystallized from chloroform–hexane: mp 115.5–117°; ν_{OH} 3540 cm^{-1}; nmr ($CDCl_3$) δ 2.5 (s, 1), 6.3 (s, 1), 6.4 (s, 1), 7.1–8.2 (m, 14).

Anal. Calcd for $C_{21}H_{17}NO_3S$: C, 69.41; H, 4.72; N, 3.86. Found: C, 69.45; H, 4.79; N, 3.84.

1-(1-Benzenesulfonylindol-2-yl)-4-methoxyphenylmethanol (13).—A procedure analogous to that for 12 gave 13 (2.55 g, 65%) as a white solid: mp 126–127° after recrystallization from methylene chloride–hexane; ν_{OH} 3560 cm^{-1}; nmr ($CDCl_3$) δ 3.75 (s, 3), 6.3 (s, 1), 6.38 (s, 1), 6.78 (d, 2, J = 8 Hz), 7.0–8.15 (m, 11).

Anal. Calcd for $C_{22}H_{19}NO_4S$: C, 67.17; H, 4.87; N, 3.56. Found: C, 67.25; H, 4.91; N, 3.59.

1-(1-Benzenesulfonylindol-2-yl)-2-pyridylmethanol (14).—A solution of 2-LiBSI (5 mmol) was prepared in THF and brought to room temperature. A solution of pyridine-2-carboxaldehyde (0.54 g, 5 mmol) in THF was added dropwise. The resulting solution was stirred at room temperature for 15 min and then poured into water. After isolation by extraction, 14 was purified by elution from a Florisil column with 10% ether in benzene (0.59 g, 32%) and recrystallized from methanol: mp 145–147°; ν_{OH} 3180 cm^{-1}; nmr (DMSO-d_6) δ 6.42 (s, 1), 6.53 (s, 1), 6.2–6.7 (broad, 1), 7.0–8.1 (m, 12), and 8.45 (d, 1, J = 4 Hz).

Anal. Calcd for $C_{20}H_{16}N_2O_3S$: C, 65.92; H, 4.43; N, 7.69. Found: C, 65.97; H, 4.49; N, 7.61.

1-(1-Benzenesulfonylindol-2-yl)-1-phenylethanol (15).—To a solution of 2-LiBSI (10 mmol) in TMEDA was added acetophenone (1.3 g, 11 mmol). After 10 min the reaction mixture was poured into water and the product (2.42 g, 64%) was isolated by extraction: mp 129–131° after recrystallization from methylene chloride–hexane; ν_{OH} 3520 cm^{-1}; nmr ($CDCl_3$) δ 1.92 (s, 3), 5.42 (s, 1), 6.87 (s, 1), 7.0–8.2 (m, 14).

Anal. Calcd for $C_{22}H_{19}NO_3S$: C, 70.02; H, 5.07; N, 3.71. Found: C, 70.04; H, 5.10; N, 3.73.

1-(1-Benzenesulfonylindol-2-yl)-1-(4-methoxyphenyl)ethanol (16).—To a solution of 2-LiBSI (10 mmol) in TMEDA was added dropwise a THF solution of 4-methoxyacetophenone (1.6 g, 11 mmol) and the reaction mixture was stirred at room temperature for 4 hr. After isolation by extraction with ether, 16 was purified by elution from silica gel with benzene (1.4 g, 35%) and recrystallized from methylene chloride–hexane: mp 137–139°; ν_{OH} 3520 cm^{-1}; nmr ($CDCl_3$) δ 1.9 (broad s, 3), 2.72 (s, 3), 5.38 (broad s, 1), 6.55–7.7 (m, 13), and 7.8–9.1 (m, 1).

Anal. Calcd for $C_{23}H_{21}NO_4S$: C, 67.81; H, 5.20; N, 3.44. Found: C, 67.86; H, 5.21; N, 3.50.

1-(1-Benzenesulfonylindol-2-yl)-1-(4-pyridyl)ethanol (17).—A solution of 4-acetylpyridine (1.3 g, 11 mmol) was added at room temperature to a solution of 2-LiBSI in TMEDA. The suspension which resulted was stirred at room temperature overnight and then poured into water. After isolation by extraction with methylene chloride, the product was obtained as a solid by trituration with ether (1.31 g, 35%) and recrystallized from chloroform–hexane: mp 229–230°; ν_{OH} 3140 cm^{-1}; nmr (DMSO-d_6) δ 1.8 (s, 3), 3.32 (s, 1), 6.02 (s, 1), 7.0–8.15 (m, 12), and 8.15–8.7 (broad, 2).

Anal. Calcd for $C_{21}H_{18}N_2O_3S$: C, 66.66; H, 4.80; N, 7.40. Found: C, 66.44; H, 4.89; N, 7.34.

1-Benzenesulfonyl-2-indolyl Phenyl Ketone (18).—A solution of benzoyl chloride (1.41 g, 10 mmol) in THF was cooled to

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−60° and a THF solution of 2-LiBSI was added rapidly. The cooling bath was then removed and the solution was allowed to come to room temperature and stirred for 1 hr. After extraction with ether and evaporation, **18** was obtained as a solid (2.35 g, 65%) by trituration with ether and recrystallized from chloroform–hexane: mp 142–144°; ν_{CO} 1660 cm^{-1}; nmr ($CDCl_3$) δ 6.87 (s, 1), 7.15–7.65 (m, 9), and 7.8–8.2 (m, 5).

Anal. Calcd for $C_{21}H_{15}NO_3S$: C, 69.80; H, 4.18; N, 3.88. Found: C, 69.85; H, 4.24; N, 3.83.

1-Benzenesulfonyl-2-indolyl 3-Pyridyl Ketone (19).—A solution of nicotinoyl chloride[21] (12.0 g, 85 mmol) in THF was cooled to −60° and 2-LiBSI (80 mmol) was added. The reaction mixture was allowed to warm to room temperature over 1 hr and then hydrolyzed by pouring into 0.04 *N* sodium hydroxide. The product was extracted with ether and purified by elution from silica gel with 1:2 ether–benzene, giving **19** (17.5 g, 60%) after trituration with ether: mp 128–129° after recrystallization from methylene chloride–hexane; ν_{CO} 1670 cm^{-1}; nmr ($CDCl_3$) δ 6.97 (s, 1), 7.2–7.65 (m, 8), 7.85–8.3 (m, 4), 8.75 (d of d, 1, J = 2, 5 Hz), 9.1 (d, 1, J = 2 Hz).

Anal. Calcd for $C_{20}H_{14}N_2O_3S$: C, 66.29; H, 3.89; N, 7.73. Found: C, 66.41; H, 3.96; N, 7.59.

Ethyl 1-Benzenesulfonylindole-2-carboxylate (20).—A THF solution of ethyl chloroformate (0.82 ml, 11 mmol) was treated at −60° with a THF solution of 2-LiBSI (10 mmol). The reaction mixture was poured into dilute alkaline brine and extracted with methylene chloride. Evaporation and trituration of the residue gave **20** (2.37 g, 75%): mp 89–91° after recrystallization from methanol; nmr (DMSO-d_6) δ 1.3 (t, 3), 4.35 (q, 2), and 7.2–8.2 (m, 10).

Anal. Calcd for $C_{17}H_{15}NO_4S$: C, 62.00; H, 4.59; N, 4.25. Found: C, 61.85; H, 4.65; N, 4.29.

1-Benzenesulfonylindole-2-carboxylic Acid (21).—A solution of 2-LiBSI (10 mmol) in THF was poured into an ether slurry of Dry Ice. The resulting mixture was acidified and the product was isolated by extraction with methylene chloride and evaporation (1.9 g, 63%): mp 188° dec after recrystallization from methylene chloride–hexane; ν_{OH} 3300–2300, ν_{CO} 1720 cm^{-1}; nmr (CH_3OH) δ 6.8–7.3 (m) and 7.45–7.8 (m).

Anal. Calcd for $C_{15}H_{11}NO_4S$: C, 59.80; H, 3.68; N, 4.65. Found: C, 59.89; H, 3.70; N, 4.64.

2-Indolyl Phenyl Ketone (22) from 2-LiBSI and Ethyl Benzoate.—A solution of ethyl benzoate (0.9 g, 6 mmol) in THF cooled in an ice–acetone bath was treated with a solution of 2-LiBSI (5 mmol) in TMEDA. After the addition, the solution was stirred for 0.5 hr, then poured into excess water. After isolation by extraction with ether, **22** was purified by elution from a silica gel column with 30% ether in hexane (0.29 g, 26%). The product was identified by melting point and comparison of its infrared spectrum with that of an authentic sample.[22]

2-Indolyl Phenyl Ketone (22) from 2-LiBSI and Benzonitrile.—A solution of 2-LiBSI (10 mmol) in ether was treated at room temperature with benzonitrile (1.03 g, 10 mmol) in ether solution. After 30 min at room temperature the reaction mixture was hydrolyzed with ammonium chloride solution. The product was isolated by extraction with ether. Trituration of the crude product gave a solid **27** described below. Chromatography of the ether-soluble portion of the product gave **22** (0.65 g, 30%), mp 147–148°, having an infrared spectrum identical with that of an authentic sample.

The maximum yield of **27** (1.6 g, 52%) was obtained when 2-LiBSI was added to a THF solution of benzonitrile at −60°. Recrystallization from methylene chloride–hexane gave pure material: mp 140–142°; ν_{NH} 3410, 3270 cm^{-1}; nmr ($CDCl_3$) δ 5.60 (d, 1, J = 2 Hz), 6.58 (s, 1), 7.1–7.7 (m, ~18–20), 8.0–8.2 (m, 2), 9.1 (broad s, 1). At 200° the mass spectrum was essentially identical with that of benzenesulfonamide, *m/e* 157, 141, 93, 77, and 51. At higher temperatures a weak peak at 460 ($P^+ - 157$) was observed.

Anal. Calcd for $C_{35}H_{27}N_3O_4S_2$: C, 68.06; H, 4.41; N, 6.80. Found: C, 67.94; H, 4.54; N, 6.74.

2-Indolyl 4-Pyridyl Ketone (23) from 2-LiBSI and Ethyl Isonicotinate.—A solution of 2-LiBSI in TMEDA (5 mmol) was added to a solution of ethyl isonicotinate (1.51 g, 10 mmol) in THF. The reaction mixture was stirred at 35° for 4 hr and then poured into water. After isolation by extraction with ether **23** was purified by elution from a silica gel column with 3:5 ether–hexane (0.34 g, 31%). The product was identified by melting point and comparison of the infrared spectrum with that of authentic material.[23]

2-Indolyl 4-Pyridyl Ketone from 2-LiBSI and 4-Cyanopyridine.—A solution of 4-cyanopyridine (0.52 g, 5 mmol) in ether was added dropwise at room temperature to a solution of 2-LiBSI (5 mmol) in ether. The solution was refluxed for 8 hr and then hydrolyzed with ammonium chloride solution. The product was isolated by extraction with methylene chloride and purified by elution from Florisil by 1:9 ether–benzene (0.58 g, 26%). The infrared spectrum was identical with that of an authentic sample.[23]

2-Indolyl 3-Pyridyl Ketone (24).—A solution of ethyl nicotinate (1.8 g, 12 mmol) in THF at 45° was treated with 2-LiBSI (10 mmol) in THF. After stirring at 45° for 1 hr the product was isolated by extraction with ether and purified by elution from silica gel with 1:2:2 chloroform–ether–benzene (0.50 g, 22%). Recrystallization from 95% ethanol gave **24**: mp 171–173°; ν_{CO} 1630 cm^{-1}; nmr ($CDCl_3$) δ 6.95–7.85 (m, 7), 8.28 (d, 1, J = 7 Hz), 8.5–9.5 (broad, 1), and 12.15 (broad s, 1).

Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.44; H, 4.65; N, 12.47.

In one run in which a higher 2-LiBSI concentration was employed, elution of the column with 10% ether–benzene gave 1-benzenesulfonyl-2,2′-biindole, **28** (1.0 g, 11%): mp 182–184° after recrystallization from ethanol; ν_{NH} 3450, 3000 cm^{-1}; nmr (acetone-d_6) δ 6.8 (d, 1, J = 2 Hz), 7.0–7.9 (m, 14), 8.4 (broad s, 1).

Anal. Calcd for $C_{22}H_{16}N_2O_2S$: C, 70.96; H, 4.33; N, 7.52. Found: C, 70.89; H, 4.40; N, 7.45.

Refluxing a suspension of **28** (180 mg, 0.48 mmol) for 4 hr with 5 ml of methanol and 1 ml of 2 *N* sodium hydroxide resulted in the formation of **29**, which was isolated by filtration. Spectral evidence suggested the assigned 2,2′-biindole structure: ν_{NH} 3420 cm^{-1}; P^+ in mass spectrum, *m/e* 232; nmr (DMSO-d_6) δ 6.8–7.8 (m), 11.45 (s); $\lambda_{max}^{95\%\ EtOH}$ 224, 334, 352 nm (lit.[12] 224, 270, 333, 351 nm). Recrystallization from ethyl acetate gave a colorless solid, mp 301–305° (lit.[12] mp 308–310°).

2-Indolyl 2-Pyridyl Ketone (25).—A solution of 2-cyanopyridine (1.04 g, 10 mmol) in ether was added dropwise at room temperature to a solution of 2-LiBSI (10 mmol) in ether. The mixture was refluxed for 8 hr and then hydrolyzed with ammonium chloride solution. The product was isolated by extraction with chloroform, purified by elution from a silicic acid column with 1:9 ether–benzene (0.81 g, 36%), and crystallized from ether–hexane, mp 132–135° (lit.[23] mp 134.5–136°). The infrared spectrum was identical with that of an authentic sample.

Cleavage of the Methoxymethyl Substituent. 23 from 11.—A mixture of **11** (100 mg, 0.36 mmol), acetic anhydride (10 ml), lithium bromide (0.5 g), and boron trifluoride etherate (1 ml) was stirred at room temperature for 48 hr. The reaction mixture was cautiously hydrolyzed using crushed ice and extracted thoroughly with ether. The ether extracts were washed with sodium bicarbonate solution, dried, and evaporated leaving **23** (66 mg, 86% yield), identified by melting point and infrared comparison with an authentic sample.

Hydrolysis of the Benzenesulfonyl Group. 1-(2-Indolyl)-phenylmethanol (30) from 12.—A solution of **12** (0.18 g, 0.50 mmol) was heated at steam bath temperature with a 5:1 methanol–2 *N* sodium hydroxide mixture for 8 hr. The product was isolated by extraction with ether and purified by preparative layer chromatography (0.098 g, 88%): ν_{OH} 3650–3150 cm^{-1}; nmr ($CDCl_3$) δ 2.7 (broad s, 1), 5.7 (s, 1), 6.15 (d, 1, J = 3 Hz), 6.9–7.6 (m with prominent s at 7.25, 9), and 8.15 (broad s, 1).

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C. 80.96; H, 5.82; N, 6.31.

1-(2-Indolyl)-1-(4-methoxyphenyl)methanol (31) from 13.—A solution of **13** (1.97 g, 5.0 mmol) was heated at steam-bath temperature for 12 hr in methanol (50 ml) and 2 *N* sodium hydroxide (10 ml). The product was isolated by extraction with ether and evaporation (1.03 g, 81%): mp 98–100° after recrystallization from methylene chloride–hexane; ν_{NH} 3430, ν_{OH} 3350 cm^{-1} (broad); nmr ($CDCl_3$) δ 3.0 (broad s, 1), 3.7 (s, 3), 5.7 (broad s, 1), 6.15 (d, 1, J = 3 Hz), 6.75 (d, 2, J = 8 Hz), 6.9–7.6 (m, 6), and 8.2 (broad s, 1).

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.81; H, 6.01; N, 5.62.

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2-Indolyl Phenyl Ketone (22) from 18.—A suspension of **18** (0.18 g, 0.50 mmol) in 8 ml of ethanol and 2 ml of 2 *N* sodium hydroxide was refluxed for 2 hr. The reaction mixture was diluted with water and **22** was isolated by extraction with chloroform (0.107 g, 97%). The melting point and infrared spectrum were identical with those of pure **22**.

2-Indolyl 3-Pyridyl Ketone (24) from 19.—A suspension of **16** (7.6 g, 21 mmol) in a solution of 200 ml of methanol and 40 ml of 2 *N* sodium hydroxide was refluxed until hydrolysis was complete (20 hr). The solution was adjusted to pH 8 and the methanol was evaporated. Extraction with methylene chloride gave **24** (6.3 g, 83%), mp 166–171°, having an infrared spectrum identical with that of pure **24**.

Acknowledgment.—This research was supported by NSF Grant GP-19374 and by NCI Grant 1A12940-01.

Registry No.—**1a**, 40899-68-1; **1b**, 40899-69-2; **1c**, 3377-71-7; **1d**, 40899-71-6; **1e**, 17983-42-5; **1f**, 40899-73-8; **2**, 40899-74-9; **3**, 40899-75-0; **4**, 40899-76-1; **5**, 40899-77-2; **6**, 40899-78-3; **7**, 40899-79-4; **8**, 40899-80-7; **9**, 40899-81-8; **10**, 40899-82-9; **11**, 40899-83-0; **12**, 40899-84-1; **13**, 40899-85-2; **14**, 40899-86-3; **15**, 40899-87-4; **16**, 40899-88-5; **17**, 40899-89-6; **18**, 40899-90-9; **19**, 40899-91-0; **20**, 40899-92-1; **21**, 40899-93-2; **22**, 1022-86-2; **24**, 40899-94-3; **25**, 24512-42-3; **26**, 40899-96-5; **27**, 40899-97-6; **28**, 40899-98-7; **29**, 40899-99-8; **30**, 40900-00-3; **31**, 40900-01-4; 2-LiMMI, 40900-02-5; 2-LiBSI, 40900-03-6; indole, 120-72-9; methoxymethyl chloride, 107-30-2; benzyloxymethyl chloride, 3587-60-8; benzyl chloride, 100-44-7; benzenesulfonyl chloride, 98-09-9; trimethylchlorosilane, 75-77-4; *tert*-butyldimethylchlorosilane, 18162-48-6; *N*-methylformanilide, 93-61-8; benzonitrile, 100-47-0; 4-methoxybenzonitrile, 874-90-8; 2-cyanopyridine, 100-70-9; 4-cyanopyridine, 100-48-1; benzaldehyde, 100-52-7; 4-methoxybenzaldehyde, 123-11-5; pyridine-2-carboxaldehyde, 1121-60-4; acetophenone, 98-86-2; 4-methoxyacetophenone, 100-06-1; 4-acetylpyridine, 1122-54-9; benzoyl chloride, 98-88-4; nicotinoyl chloride, 10400-19-8; ethyl chloroformate, 541-41-3; ethyl benzoate, 93-89-0; ethyl nicotinate, 614-18-6.

Syn–Anti Isomerization of *N*-(*p*-Tolyl)imines of Ferrocenyl, Ruthenocenyl, and (Cyclobutadienyliron Tricarbonyl) Phenyl Ketones

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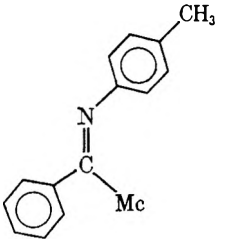
The *N*-(*p*-tolyl)imines of ferrocenyl, ruthenocenyl, and (cyclobutadienyliron tricarbonyl) phenyl ketones were prepared in moderately good yield. Studies of their syn–anti isomerization using the dnmr technique allowed the determination of their free energies of activation. The validity of approximate equations to determine free energies of activation as well as the conditions necessary for successful complete line-shape analysis are discussed.

Recently we reported[1] evidence for the syn–anti isomerization of imines I and II. In that report we

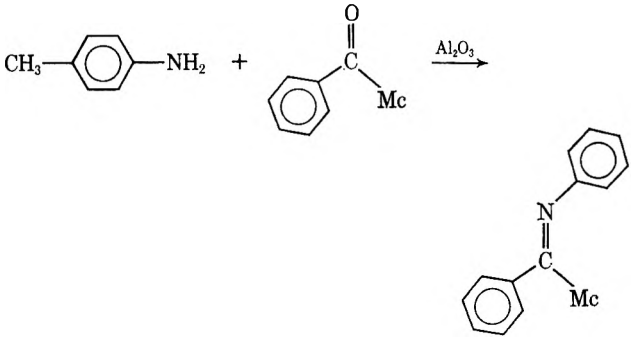


I, Mc = ferrocenyl
II, Mc = ruthenocenyl
III, Mc = cyclobutadienyliron tricarbonyl

drew attention to the approximate nature of the dnmr measurements used as supporting evidence for the isomerization. In this paper we not only extend our measurements to compound III, but also bring to light our attempts to apply complete line-shape analysis to the dynamic nuclear magnetic resonance (dnmr) data. In addition, the preparations of compounds I, II, and III are discussed.

Results and Discussion

The three compounds used in this study were prepared using the method of Hetnarski and Grabowski[1,2] in which *p*-toluidine and the appropriate phenone compound were condensed in the presence of aluminum oxides. This method originally had been successfully applied[2] only to ferrocene derivatives. We have expanded the method's utility and it appears to be fairly



general for the reaction of metallocene and metallocene-like ketones with aromatic amines. The beauty of the method is that it can be carried out under mild conditions (refluxing toluene), that it is quite clean (followed by thin layer chromatography), and that work-up is fairly simple. Purified yields range from 40 to 50%.

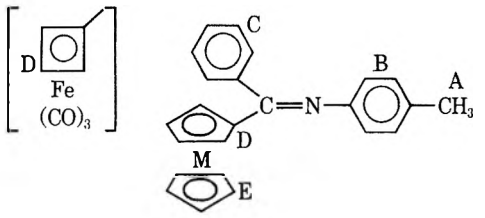
Characterization of I–III was accomplished using infrared, mass, and nuclear magnetic resonance spectroscopy and elemental analysis. Examination of both ir and nmr spectra made it clear that a mixture of isomers had been obtained. As examples: Compound I and II have doubled signals of unequal intensity assigned to the *p*-methyl group and to the unsubstituted cyclopentadienyl hydrogens. Compound III has two signals for its *p*-methyl group as well as doubled signals in the cyclobutadienyl group. It should be noted that we have observed other signal doubling, but that it occurs with protons of low intensity and high splitting and is consequently less dramatic. In Table I we have compiled the nmr data for compounds I–III. The unequal intensities of the signals indicated in Table I show that in compounds I and II one isomer predominates by six- to tenfold while the isomer ratio in III is

(1) R. Damrauer and T. E. Rutledge, *J. Organometal. Chem.*, **29**, C 9 (1971).

(2) B. Hetnarski and Z. Grabowski, *Bull. Acad. Pol. Sci.*, **17**, 391 (1969).

Table I

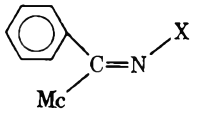
Room-Temperature Nmr Spectra of I, II, and III



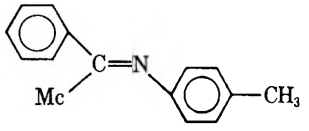
	A[a,b]	B	C	D	E
I	2.17 (s) [10][c]			4.38 (t)	4.12 (s) [7]
	2.37 (s) [1]	6.70 (q)	7.20 (s)	4.65 (t)	4.22 (s) [1]
II	2.16 (s) [6]			4.70 (t)	4.62 (s) [6]
	2.30 (s) [1]	6.67 (q)	7.15 (s)	4.93 (t)	4.53 (s) [1]
III	2.18 (s) [1]		6.68 (s)	3.67 (s)	
			7.17 (m)	4.07 (s)	
	2.35 (s) [1.3]	6.62 (q)	7.43 (m)	4.32 (s)	
				4.48 (s)	

[a] δ in parts per million downfield from TMS; $CDCl_3$ solvent. [b] s = singlet, t = triplet, q = quartet, m = multiplet. [c] Relative intensities in brackets.

more nearly equal. To attempt to ascertain the identity of each isomer, we studied the solution and solid infrared spectra of I–III. Curtin and coworkers[3] have assigned the syn and anti configuration to isomers of benzophenone imines basing their judgment on the observation that in disubstituted olefins (styrene-like) the hydrogen deformation band of the monosubstituted phenyl ring occurs at higher frequency in that isomer with an atom or group cis to the phenyl ring. As applied to imines the isomer with the higher hydrogen deformation frequency will be syn. Applying Curtin's



criterion to compounds I and II it would appear as though the anti isomer i predominates in solution



i

(Table II). We are hesitant to accept this based on earlier work[4] in which the bulkiness of the ferrocenyl

Table II

Infrared Stretching Frequencies of I, II, and III in the 700-cm^{-1} Region

	Solution (CS_2), cm^{-1}		Solid (KBr), cm^{-1}	
I	693 (m)[a]	703 (sh)	702 (m)	714 (s)
II	692 (m)	699 (sh)	701 (m)	710 (s)
III	700 (s)	720 (vw)	690 (s)	702 (vw)

[a] sh = shoulder, s = strong, m = medium, vw = very weak.

group was shown to be an important factor in determining the dynamic processes of ferrocenyl amides. It seems prudent to state that, although it is quite clear that one isomer predominates in I and II (and it appears to be the same isomer), we are not convinced that Curtin's criterion applies to compounds I–III. The solid-phase infrared results (Table II) further complicate isomeric assignment since in these the intensities of the predominant peaks are reversed.

To obtain information on the dynamics of the syn–anti isomerization process of I–III we studied their nmr spectra as a function of temperature. All of the spectral changes to be discussed have been shown to be reversible. We have witnessed a coalescence of all of the doubled signals mentioned previously, but for the purposes of dnmr analysis have focused our attention on the *p*-methyl group. The coalescence temperatures for compounds I–III are 54, 61, and 91°, respectively.

Since only few data[5,6] exist on the activation parameters for syn–anti isomerizations of ketimines, we have attempted complete line-shape analysis on compounds I–III. The introduction of experimental parameters into the standardly modified Block equations[7,8] generated a series of theoretical line shapes. These were visually[9] compared with the experimental curves, thus allowing rate constant assignment to the experimental data. Activation parameters generated by this method are compiled in Table III.[10] The entropies of activation are suspiciously large (in absolute value) for a process whose transition state does not involve either bond making or breaking or large changes in nonbonded interactions.[11] Raban and Carlson[11] in commenting upon the reliability of activation entropy data generated by complete line-shape analysis suggest that these data are highly suspect *unless* the temperature range over which the analysis is made exceeds 100°. Our data, obtained over a fairly small temperature range, appear unreliable in this respect. The free energies of activation, however, are indicative of the now common experience[11] that complete line-shape analysis provides quite reasonable free energies of activation.

Table III

Activation Parameters by Visual Correlation of Experimental Data at 25°

Compd	$\Delta H^{\ddagger}$, kcal/mol[a]	$\Delta S^{\ddagger}$, eu	$\Delta G^{\ddagger}$, kcal/mol	K[b]
I	27.0	25.1	19.6	0.14
II	23.7	14.7	19.3	0.15
III	17.6	−8.6	20.2	1.28

[a] k_A for A → B. [b] $K = P_B/P_A$ where A is upfield of B, and P_A is the population of A.

Because of our failure to obtain reliable activation entropies for the syn–anti isomerization process, we explored the utility of the approximate equations in evaluating $\Delta G^{\ddagger}$ at the coalescence temperature. Table IV details the results of calculations carried out by two approximation procedures.[12,13] The first[12] strictly applies only to unsplit coalescing signals of equal

(3) (a) D. Y. Curtin and J. W. Hausser, *J. Amer. Chem. Soc.*, **83**, 3474 (1961); (b) D. Y. Curtin, E. J. Grubbs, and C. G. McCarty, *J. Amer. Chem. Soc.*, **88**, 2775 (1966).

(4) R. Damrauer, *J. Organometal. Chem.*, **32**, 121 (1971).

(5) C. G. McCarty in "The Chemistry of the Carbon–Nitrogen Double Bond," S. Patai, Ed., Wiley-Interscience, New York, N. Y., 1970.

(6) H. Kessler, *Angew. Chem., Int. Ed. Engl.*, **9**, 219 (1970).

(7) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956).

(8) G. Binsch, *Top. Stereochem.*, **3**, 97 (1968).

(9) A program to normalize experimental curves for easy visual comparison with theroetical curves was used. Computer-aided least square fitting of experimental and theroetical data did not improve on visual data comparison.

(10) See paragraph at end of paper regarding supplementary material.

(11) M. Raban and E. Carlson, *J. Amer. Chem. Soc.*, **93**, 685 (1971).

(12) D. Kost, E. H. Carlson, and M. Raban, *Chem. Commun.*, 656 (1971).

(13) H. Shanan-Atidi and K. H. Bar-Eli, *J. Phys. Chem.*, **74**, 961 (1970).

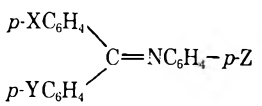
TABLE IV
COMPARISON OF FREE ENERGIES[a] OF ACTIVATION DETERMINED BY VARIOUS METHODS

	Visual[b] complete line shape at T_c	Approximate[c] expression at T_c	Approximate[d] expression at T_c
I	18.9	17.2	18.2
II	18.8	17.6	18.4
III	20.8	19.0	19.0

[a] In kcal/mol. [b] A ⇌ B from rate constants expressed in radians/sec. [c] $\Delta G^{\ddagger}$ at $T_c = -RT \ln [k_c h/kT_c]$; $k_c = \pi\Delta\nu/\sqrt{2}$. [d] See H. Shanan-Atidi and K. H. Bar-Eli, *J. Phys. Chem.*, **74**, 961 (1970).

intensity while the latter[13] has been applied to unsplit signals of unequal intensity. It is clear from the table that the latter, the method of Shanan-Atidi and Bar-Eli,[13] gives results more closely in agreement with the complete line-shape results. However, the uncertainties resulting from the small temperature range studied for compounds I–III indicate that the complete line-shape analysis offers no advantage over the approximate methods. The similar $\Delta G^{\ddagger}$ values for the three methods in Table IV give us confidence in their validity, as does the now common experience of such similarities in others' analyses.[11,12]

Studies relating to the mechanism(s) of syn–anti isomerization of imines are numerous.[5] Two limiting mechanisms have been considered seriously with imines: (1) a lateral shift or inversion mechanism through a linear, –N=C<, transition state and (2) a rotational mechanism with a transition state resembling either $-\dot{N}-\dot{C}<$ or $-N^{-}-C^{+}<$. In the lateral shift the substituent on nitrogen shifts from one isomeric environment to the other while the π bond remains intact and nitrogen rehybridizes to sp in the transition state; the rotational mechanism occurs through the "single-bonded" transition state by "free" rotation. Because the activation energies necessary for a homolytic rotational isomerization are expected to be high, it is generally thought[5] that such a pathway is unlikely for most imines. Both the heterolytic rotational and lateral shift pathways have been seriously considered. Evidence[14,15] for the rotational mechanism rests on substituent studies on compounds like $C_6H_5N{=}CX_2$ (where X = CH_3, OCH_3, SCH_3, etc.). Free energies of activation ($\Delta G^{\ddagger}_{Tc}$) drop dramatically as X's conjugative ability increases as presumably the mechanism shifts to purely rotational. The $\Delta G^{\ddagger}$'s range from 21 kcal/mol for a carbon to 12 kcal/mol for a nitrogen substituent. The lateral shift mechanism[3,5] appears to operate with compounds like ii. Substituents X and Y have very



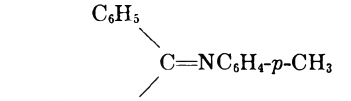
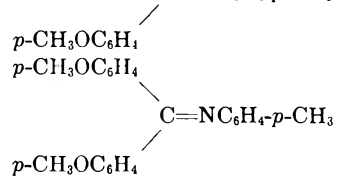
ii

small effects on activation energies (ρ = 0.1) while Z's effects (ρ = 1.5) are only slightly larger.[3] In all, E_a's between 17 and 20 kcal/mol are obtained.

Since no well-substantiated case for a rotational mechanism exists when X is a carbon substituent, we decided to attach to this position a metallocene group. We chose the ferrocenyl, ruthenocenyl, and cyclobutadienyliron tricarbonyl compounds I–III because we felt that the well-known[16–19] tendency of these to stabilize an adjacent electron-deficient center would stabilize a dipolar transition state like $>C^{+}-N^{-}-$. In addition, we designed compounds I–III to be comparable with the isomerization data of other imines.[3]

Table V summarizes our data as well as some of that of Curtin and coworkers[3] on the isomerization of

TABLE V
FREE ENERGIES OF ACTIVATION[a] OF VARIOUS PHENONES

Compd	$\Delta G^{\ddagger}$[b] at T_c
I	18.2
II	18.4
III	19.0
	18.5
	18.8

[a] A ⇌ B from rate constants expressed in radians/sec. [b] See H. Shanan-Atidi and K. H. Bar-Eli, *J. Phys. Chem.*, **74**, 961 (1970).

phenone arylimines (made comparable by recalculating Curtin's data[3,12,13]); although there are slight variations among results, they are not considered to be significant in view of the rather substantial variations we have seen earlier in treating the data using various methods of analysis. We believe, therefore, that the free energies of all five compounds listed in Table V are substantially the same and that the effect of the metallocene or metallocene-like substituent is not noticeably different from that of an aromatic substituent. As a result we feel that these groups are not in any perceptible way stabilizing a dipolar rotation transition state. We conclude based on our data and its comparison to that of Curtin that the syn–anti isomerization for compounds I–III occurs through a lateral shift mechanism.

Experimental Section

General Comments.—Elemental analyses were performed by Huffman Laboratories, Wheatridge, Colo. Ir spectra were recorded using either a Perkin-Elmer 237B grating ir spectrophotometer or a Beckman IR-12. The nmr spectra were recorded using a Varian A-60A high-resolution spectrometer. Chemical shifts are reported in parts per million downfield from tetramethylsilane. All nmr temperature studies were performed using a Varian Associates 6040 variable temperature controller on degassed samples under prepurified nitrogen. Temperature measurements were made using either the methanol (<30°) or ethylene glycol (>30°) separation–calibration method. Such measurements were carried out before and after each temperature run. Mass spectra were recorded on an AEI MS-12 mass spectrometer. All reactions were carried out under an atmosphere of prepurified nitrogen. Boiling points were recorded at prevailing pressure (~640 mm) unless otherwise indicated. Boiling and melting points are uncorrected.

(14) N. P. Marullo and E. H. Wagener, *Tetrahedron Lett.*, 2555 (1969).
(15) M. Raban, *Chem. Commun.*, 1415 (1970).
(16) E. A. Hill and R. Wiesner, *J. Amer. Chem. Soc.*, **91**, 509 (1969).
(17) M. Cais, *Rec. Progr.*, **27**, 177 (1966).
(18) S. P. Gubin and A. A. Lubovick, *J. Organometal. Chem.*, **22**, 183 (1970).
(19) L. Watts, Jr., Ph.D. Dissertation, University Microfilm Inc., Ann Arbor, Mich., 1966, No. 66-7383.

Preparation of the *N*-(*p*-Tolyl)imine of Ferrocenyl Phenyl Ketone (I).—Into a single-necked 50-ml flask equipped with a condenser, nitrogen inlet tube, and magnetic stirring bar were charged 0.25 g (0.86 mmol) of benzoylferrocene (Arapahoe Chemical Co.), 0.10 g (0.95 mmol) of *p*-toluidine [sublimed at 40° (0.01 mm) from Eastman Practical], 97 mg (0.95 mmol) of aluminum oxide (Merck acid washed), and 25 ml of dry toluene. The mixture was refluxed for 4 days; daily additions of 0.1 g of *p*-toluidine were required to maximize the rate of formation of imine. Monitoring by thin layer chromatography indicated that an equilibrium mixture had formed after 4 days. The hot reaction mixture was filtered through a sintered glass funnel and the filtrate yielded a red residue (0.42 g) upon rotary evaporation at 50° (15 mm). Addition of hexane cause the residue to crystallize. Excess *p*-toluidine was removed by sublimation at 40° (0.01 mm). Column chromatography using benzene as eluent yielded 0.27 g (83%) of imine (fastest moving band) as well as some unreacted ketone.

A large-scale experiment carried out on 9.20 g (31.6 mmol) of benzoylferrocene yielded 5.0 g (42%) of pure imine (recrystallization from hexane gave mp 138–139°): ir ($CDCl_3$) 3107, 3080, 2941, 2880, 1605, 1591, 1575, 1494, 1452, 1285, 1097, 944, 958, 917, and 872 cm^{-1}; nmr ($CDCl_3$), see Table I; mass spectrum (70 eV) *m/e* (rel intensity) 381 (4), 380 (31), 379 (100), 378 (10), 377 (12), 314 (29), 121 (10), and 69 (10).

Anal. Calcd for $C_{24}H_{21}FeN$: C, 76.00; H, 5.58. Found: C, 75.83; H, 5.71.

Preparation of the *N*-(*p*-Tolyl)imine of Ruthenocenyl Phenyl Ketone (II).—Into a 250-ml single-neck flask equipped with a condenser, nitrogen inlet tube, and magnetic stirring bar were charged 2.86 g (8.5 mmol) of ruthenocenyl phenyl ketone,[20] 2.74 g (25.6 mmol) of *p*-toluidine (Eastman Practical, recrystallized), 8.72 g (85.4 mmol) of aluminum oxide, and 100 ml of dry toluene. Thin layer monitoring showed after reflux for 2 days that the reaction was complete. The mixture was filtered through a sintered glass filter and rotary evaporated. Addition of petroleum ether caused the residue to crystallize. Unreacted *p*-toluidine was removed by sublimation at room temperature (0.05 mm) and the sublimation residue was chromatographed on alumina. With benzene as eluent three bands were readily distinguishable and separable. The fastest moving was ruthenocene, the next, the imine, and the slowest, ruthenocenyl phenyl ketone. We obtained 0.65 g (23%) of starting ketone as well as 1.66 g (47%) of the imine after recrystallization from petroleum ether: mp 100–101°; ir ($CDCl_3$) 3100, 2977, 1608, 1491, 1286, 1094, 997, 974, 878, and 864 cm^{-1}; nmr ($CDCl_3$), see Table I; mass spectrum (70 eV) *m/e* (rel intensity) 429 (3), 428 (16), 427 (50), 426 (36), 425 (100), 424 (88), 423 (78), 422 (63), 421 (28), 420 (11), 419 (14), 319 (20), 231 (14), 195 (11), 194 (55), and 167 (15).

Anal. Calcd for $C_{24}H_{21}RuN$: C, 67.91; H, 4.99. Found: C, 68.16; H, 5.24.

Preparation of the *N*-(*p*-Tolyl)imine of (Cyclobutadienyliron Tricarbonyl) Phenyl Ketone (III).—(Cyclobutadienyliron tricarbonyl) phenyl ketone[19] (5.0 g, 16.9 mmol), 5.44 g (50.8 mmol) of *p*-toluidine, 17.2 g (169 mmol) of aluminum oxide, and 100 ml of toluene were allowed to react at reflux for 3 days. The reaction and work-up were essentially the same as those described to prepare I and II with the following exceptions: (1) the reaction vessel was protected from light by aluminum foil; (2) chromatographic separation with benzene yielded in the initial fractions a mixture of starting ketone, *p*-toluidine, and imine; (3) sublimation at 30° (0.02 mm) removed ketone and *p*-toluidine; and (4) further sublimation at 60–80° (0.02 mm) yielded yellow crystals of imine. A total yield of 3.0 g (46%) of imine III was obtained: mp 110–112°; ir ($CDCl_3$) 3300, 2050, 1975, 1605, 1100, 1005, 925, and 810 cm^{-1}; nmr ($CDCl_3$), see Table I; mass spectrum (70 eV *m/e* (rel intensity) 386 (1), 385 (4), 357 (36), 329 (22), 302 (18), 301 (77), 276 (21), 275 (100), 194 (16), 173 (29), 172 (17), and 81 (10).

Anal. Calcd for $C_{21}H_{15}O_3NFe$: C, 65.48; H, 3.93. Found: C, 65.62; H, 4.17.

Comments on Variable-Temperature Nmr Studies and Analysis of Data.—Solvents used for the variable-temperature measurements (diphenyl ether and α,α,α-trifluorotoluene) showed only very slight shifts relative to $CDCl_3$. Slight discrepancies between the data in Table I and our preliminary report[1] are caused by the solvent effects. The necessary precautions for accurate dnmr work were taken[8,21] both with respect to the experimental measurements and analysis of the data.

Acknowledgments.—We would like to thank the Arapahoe Chemical Co. for gifts of ruthenocene and benzoylferrocene. We also acknowledge the support of the Research Corporation, the National Institutes of Health (through a Biomedical Grant administered by the University), the American Cancer Society (through a grant administered by the University of Colorado Medical School), the Graduate School of the University of Colorado, and University of Colorado Computing Center. Finally, we thank Professor S. Zumdahl for supplying us with the dnmr programs as well as much valuable information about their proper use.

Registry No.—*syn*-I, 40940-71-4; *anti*-I, 40940-73-6; *syn*-II, 40940-74-7; *anti*-II, 40940-75-8; *syn*-III, 40940-76-9; *anti*-III, 40940-72-5.

Supplementary Material Available.—Nmr spectra at varying temperatures will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20 × reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-3330.

(20) M. D. Rausch, E. O. Fischer, and H. Gurbert, *J. Amer. Chem. Soc.*, **82**, 76 (1960).

(21) A. Allerhand, H. S. Gutowsky, J. Jonas, and R. A. Meinzer, *J. Amer. Chem. Soc.*, **88**, 3185 (1966).

Interconversion Reactions of Aluminum Isopropoxide Polymers

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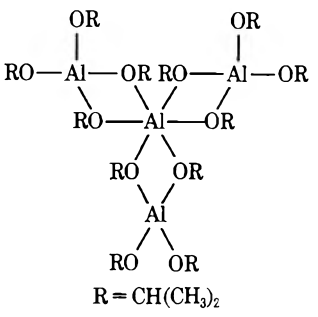
Received April 3, 1973

The interconversion reactions of the dimeric, trimeric, and tetrameric forms of aluminum isopropoxide have been studied by cryoscopic and nuclear magnetic resonance techniques. Starting from pure dimer, the first reaction is rapid equilibration with trimer, after which the tetramer is formed very much more slowly; starting from pure tetramer, a mixture of all three species is slowly formed. Rate coefficients for individual steps of the interconversion process are suggested on the basis of the fit of the overall kinetic results to a computer simulation of the reaction scheme.

It has long been known from cryoscopic studies that solid aluminum isopropoxide dissolves in benzene to give a solution in which the alkoxide is tetrameric.[1] The structure, shown in Chart I, was first put forward

CHART I



by Bradley,[2] who deduced it on the basis of his general principle of alkoxide chemistry[3] that an alkoxide undergoes the minimum degree of polymerization consistent with the maximum covalency of the metal. This structure was later confirmed by proton magnetic resonance studies of the alkoxide.[4] On melting, solid aluminum isopropoxide gives a liquid which is stable over a period of days at room temperature, the solid crystallizing out slowly. The liquid form, known as the melt, was shown to be approximately trimeric in benzene solution by cryoscopic measurements,[5] and proton magnetic resonance studies[4] showed that it had a different structure from the tetramer; the alkoxide groups of the trimer were undergoing exchange at room temperature sufficiently fast for them to be indistinguishable by nmr spectroscopy. On cooling to −39°, the methyl proton region showed two doublets, in approximately the ratio of 1:2, though the resolution obtained was insufficient to permit accurate integration of the spectrum.

A more recent investigation of the melt[6] has shown that at high temperatures it consists largely of the dimer and that, by rapid cooling of a hot solution of the melt, a solution of dimeric aluminum isopropoxide can be obtained. Studies of the dimer by proton magnetic resonance spectroscopy[6] are consistent with it having a bridged structure, similar to that of aluminum halides in the gas phase[7] and aluminum *tert*-butoxide in solution[4,5] which is shown in Chart II.

CHART II

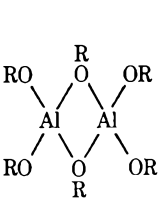
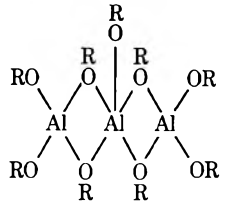


CHART III



R = CH(CH3)2

However, studies of the trimer by aluminum magnetic resonance spectroscopy[6] have led to the suggestion that the trimer has the structure shown in Chart III, in which two aluminum atoms are 4-coordinate and one is 5-coordinate. Although pentacoordinate aluminum is relatively uncommon, it has been postulated to exist in complexes of aluminum isopropoxide with ethylenediamine[8] and with β-dicarbonyl compounds,[9] and in complexes of trialkylaluminum with diamines[10] and tetramethyltetrazene.[11]

Experimental Section

Preparation of Materials.—Purification of aluminum isopropoxide was by distillation at 108.5–109.5° (0.4 mm), then the melt was allowed to crystallize slowly at room temperature;[12] solutions of the pure tetramer in dry benzene were made up and sealed in nmr tubes. Reactions were carried out in the nmr tubes, which were thermostated at appropriate temperatures between points. The tetramer remained stable in benzene solution, frozen at 0°, but the melt form could not be stabilized; so the contents of a tube were converted to melt before each run, using the heating and rapid cooling technique outlined earlier.[12]

Kinetics.—The reaction was followed by integration of the methyl proton region of the nmr spectrum recorded on a Varian A-60 spectrometer, at least 12 integrals of each spectrum being recorded and averaged. The integral of the two peaks at 102 and 96 cps from TMS, which have been shown to constitute 25% of the methyl protons of the tetramer,[4] were compared with the integral of the rest of the methyl proton peaks, which constitute 75% of the methyl proton peaks of the tetramer, and all the methyl proton peaks of the melt.[4] In this way, the amount of tetramer in the solution could be calculated. Results obtained in this way were reproducible to ±2%.

Calculation of Results.—In order to test possible mechanisms,

(1) H. Ulich and W. Nespital, *Z. Physik. Chem.*, **165**, 294 (1933).
(2) D. C. Bradley, "Metal Alkoxides," Advances in Chemistry Series, 23, American Chemical Society, Washington, D. C., 1959, p 10.
(3) D. C. Bradley, *Nature (London)*, **182**, 1211 (1958).
(4) V. J. Shiner, Jr., D. Whittaker, and V. P. Fernandez, *J. Amer. Chem. Soc.*, **85**, 2318 (1963).
(5) R. C. Mehrotra, *J. Indian Chem. Soc.*, **30**, 585 (1953).
(6) D. C. Kleinschmidt and V. J. Shiner, Jr., unpublished work.
(7) K. J. Palmer and N. Elliott, *J. Amer. Chem. Soc.*, **60**, 1852 (1938).
(8) V. J. Shiner, Jr., and D. Whittaker, *J. Amer. Chem. Soc.*, **87**, 843 (1965).
(9) R. K. Mehrotra and R. C. Mehrotra, *Can. J. Chem.*, **39**, 795 (1961).
(10) N. R. Fetter, B. Bartocha, F. E. Brinckman, Jr., and D. W. Moore, *Can. J. Chem.*, **41**, 1359 (1963).
(11) N. R. Fetter, F. E. Brinckman, Jr., and D. W. Moore, *Can. J. Chem.*, **40**, 2184 (1962).
(12) V. J. Shiner, Jr., and D. Whittaker, *J. Amer. Chem. Soc.*, **91**, 394 (1969).

details of the reaction schemes were programmed onto an E. A. I. TR-10 analog computer, and rate constants were adjusted to give the best fit with observed data. The data given in Table I were

TABLE I[a]
FORMATION AND DECOMPOSITION OF ALUMINUM ISOPROPOXIDE TETRAMER IN BENZENE SOLUTION AT 45.00°

Reaction starting from tetramer		Reaction starting from melt	
Time, hr	Tetramer, *M*	Time, hr	Tetramer, *M*
0	0.1482	0	0.0000
23	0.1424	23	0.0179
46	0.1353	46	0.0258
93	0.1248	69	0.0328
116	0.1211	92	0.0391
163	0.1152	116	0.0425
186	0.1085	162	0.0476
209	0.1065	185	0.0485
256	0.1012	Infinity	0.0536
327	0.0916		
374	0.0872		
421	0.0844		
492	0.0777		
539	0.0753		
Infinity	0.0561		

[a] Alkoxide concentration was 0.607 *M* (calculated as monomer).

used for this purpose, since the rates of reaction in both directions were slow enough to permit accurate measurement of data, but fast enough to permit the reaction to be easily followed over two half-lives.

Results and Discussion

Dimer to Trimer Interconversion.—Heating a solution of aluminum isopropoxide in toluene to 110° for 6 hr, followed by rapid cooling to the temperature of the nmr probe, gave a solution whose spectrum, measured 4 min after completion of heating, was a sharp doublet at 79 and 73 cps from TMS, together with a smaller, much broader doublet at 84 and 78 cps. On standing, the upfield doublet decayed and the downfield doublet increased in size, until an equilibrium was reached in which the latter predominated. We have already shown this solution to have a molecular weight of 587, suggesting it to be a mixture of dimer and trimer, in which the latter predominates;[4] in order to confirm that the upfield doublet results from the dimer and the downfield doublet from the trimer, changes in nmr spectrum and molecular weight were followed on samples of the same solution of aluminum isopropoxide in benzene. On the basis of the nmr data, measured at the melting point of benzene, the degree of polymerization of the solution was calculated as a function of time; these results are given in Table II.

TABLE II[a]
NMR STUDY OF ALUMINUM ISOPROPOXIDE MELT IN BENZENE

	Integral[c]		
Time,[b] min	Downfield doublet	Upfield doublet	Calculated degree of polymerization
21	17.1	18.8	2.48
43	19.1	17.6	2.52
68	18.9	18.8	2.53
93	18.9	18.8	2.53
134	24.0	14.0	2.63
344	22.7	10.0	2.69

[a] The solution used was identical with that used to obtain the data recorded in Table III. In all cases, the intergals were the average of upfield and downfield sweeps. [b] Measured from removal of tube from oven. [c] In arbitrary units.

The molecular weight was measured as a function of time at the temperature of freezing benzene by observing changes in the freezing point depression; the results obtained, given in Table III, confirm the assignment

TABLE III[a]
CRYOSCOPIC STUDY OF ALUMINUM ISOPROPOXIDE MELT IN BENZENE

Time,[b] min	Mol wt	Degree of polymerization
18	526	2.58
43	501	2.46
66	536	2.63
90	566	2.78
156	566	2.78
2520	566	2.78

[a] The solution used contained 0.153 *M* alkoxide, calculated as monomer. It was heated to 110° for 6 hr before use, then cooled rapidly in a Dry Ice–acetone bath. [b] Measured from removal of the tube from the oven.

of the upfield doublet to the dimer and the downfield doublet to the trimer.

The data show that, at the temperature of freezing benzene, the half-life for the conversion of dimer to the dimer–trimer equilibrium mixture is *ca.* 15 min; the equilibrium mixture has a degree of polymerization of 2.7, lower than that observed earlier[4] for the melt form of the alkoxide, 2.83, consistent with the latter containing some tetramer.

On account of the speed of the interconversion, compared to the rather slow method of studying it, an accurate kinetic study has not been attempted.

Tetramer to Melt Interconversion.—The term "melt" is used to describe the equilibrium mixture of dimer and trimer which was used in the experiments described below. Preliminary experiments showed that the rate of interconversion of the tetramer and melt forms of aluminum isopropoxide was very much slower than the rate of the dimer to trimer interconversion, and could conveniently be followed by nmr analysis of the reaction mixtures; the assignments of the nmr spectrum of the tetramer are given in an earlier paper.[4]

Using this method, the kinetics of formation of tetramer from melt and of formation of melt from tetramer were measured. The reactions are complex ones in which several equilibria are involved; so they would not be expected to show any simple kinetic form. Surprisingly, the data at each alkoxide concentration were found to fit a first-order rate plot over 2 half-lives. The reaction is clearly much more complex than a simple first-order reaction, but the fortuitous balance of rates and equilibria apparently combine to give "deceptively simple kinetics."

We have used this phenomenon to simplify presentation of our data, reducing them to "first-order" rate coefficients. These are quoted in Tables IV and V.

The equilibrium concentrations of the tetramer under different conditions of temperature and alkoxide concentration are listed in Table VI. These values are the average of those obtained by approaching the equilibrium from either side.

Attempts to calculate equilibrium constants on the assumption that the melt, at this stage, contained only trimer were not successful. If, however, the equilibrium mixture was assumed to contain dimer, trimer, and

TABLE IV

FIRST-ORDER RATE COEFFICIENTS FOR THE FORMATION OF TETRAMERIC ALUMINUM ISOPROPOXIDE FROM THE MELT FORM IN BENZENE SOLUTION[a]

Concn of aluminum isopropoxide, mol of monomer	$10^6 k_1$, sec^{-1} 25.00°	35.00°	45.00°
0.607	1.00	1.57	3.75
1.030	1.48	2.00	4.15
1.789	1.61	3.16	6.32

[a] Mean energy of activation was 12.0 kcal mol^{-1}.

TABLE V

FIRST-ORDER RATE COEFFICIENTS FOR THE CONVERSION OF TETRAMERIC ALUMINUM ISOPROPOXIDE TO THE MELT FORM IN BENZENE SOLUTION[a]

Concn of aluminum isopropoxide, mol of monomer	$10^6 k_1$, sec^{-1} 35.00°	45.00°	65.00°
0.607	0.292	0.810	3.69
1.030	0.438	1.008	3.92
1.789	0.544	1.354	4.90

[a] Mean energy of activation was 15.2 kcal mol^{-1}.

TABLE VI

EQUILIBRIUM CONCENTRATIONS OF TETRAMERIC ALUMINUM ISOPROPOXIDE IN BENZENE SOLUTION[a]

Concn of aluminum isopropoxide, mol of monomer	Tetramer at equilibrium, % 25.00°	35.00°	45.00°	65.00°
0.607	53.1	41.9	36.2	20.2
1.030	58.4	48.2	41.7	24.6
1.789	63.3	53.7	46.9	28.5

[a] The values are quoted as per cent of monomeric alkoxide existing as the tetramer.

tetramer simultaneously, then the equilibria [tetramer]/[trimer] = k_A and [tetramer]/[dimer] = k_B exist simultaneously. The values of k_A and k_B calculated on this basis were found to be self-consistent, and are listed in Table VII. From these, the equilibrium concentrations of each species can be calculated over the range of concentrations and temperatures covered by the kinetic studies.

TABLE VII

VALUES OF THE EQUILIBRIUM CONSTANTS, k_A AND k_B, FOR THE EQUILIBRIUM BETWEEN THE DIMERIC, TRIMERIC, AND TETRAMERIC FORMS OF ALUMINUM ISOPROPOXIDE IN BENZENE SOLUTION

Equilibrium constant	Value, l. mol^{-1} 25.00°	35.00°	45.00°	65.00°
k_A	182	27.9	4.39	0.323
k_B	26.3	6.65	8.77	3.46

The kinetic data are inconsistent with decomposition to monomer, followed by recombination of the monomer to different polymeric species. The overall reaction consists of a fast interconversion of dimer and trimer, followed by a much slower interconversion involving all three species. All possible reaction mechanisms involve at least four separate steps; so, in order to test possible mechanisms, each was programmed onto an analog computer, and then tested against the data given in Table I.

A number of mechanisms were tested in this way. Those which involved formation of a monomeric species were fairly easy to fit to the data by suitable choice of rate coefficients; in all cases, however, they predicted an equilibrium mixture containing a large concentration of monomer, which is contrary to the data in Tables VI and VII. The only mechanism tested which fitted both kinetic and equilibrium data is that given below.

$$3\ \text{dimer} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} 2\ \text{trimer}$$

$$2\ \text{trimer} \underset{k_4}{\overset{k_3}{\rightleftharpoons}} \text{hexamer}$$

$$\text{hexamer} \underset{k_6}{\overset{k_5}{\rightleftharpoons}} \text{tetramer} + \text{dimer}$$

$$2\ \text{dimer} \underset{k_8}{\overset{k_7}{\rightleftharpoons}} \text{tetramer}$$

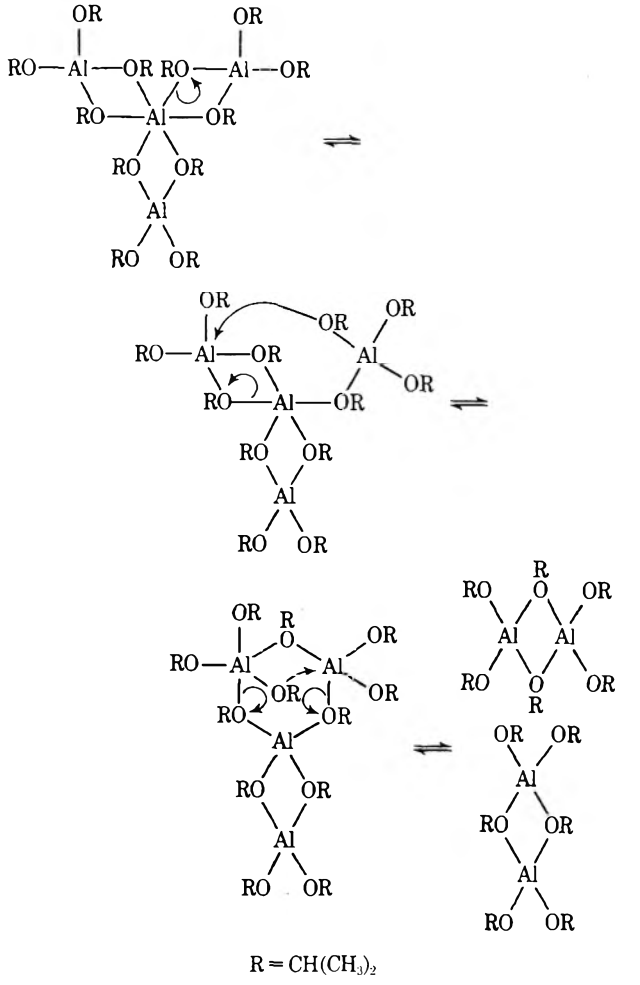
One set of rate constants which fits this to the observed data follows: k_1 is fast; k_2 is fast; $k_3 = 0.267 \times 10^{-6}$ l. mol^{-1} sec^{-1}; $k_4 = 5.6 \times 10^{-4}$ sec^{-1}; $k_5 = 5.6 \times 10^{-4}$ sec^{-1}; $k_6 = 2.82 \times 10^{-6}$ l. mol^{-1} sec^{-1}; $k_7 = 0.098 \times 10^{-6}$ l. mol^{-1} sec^{-1}; $k_8 = 0.528 \times 10^{-6}$ sec^{-1}.

The values of the other rate constants required to obtain a fit are only affected by the ratio of k_1 to k_2 and not by their absolute magnitude. Therefore k_1 and k_2 were set at large values and their ratio was adjusted so that the rate of approach to overall equilibrium was fitted by the same set of constants starting with either "melt" or tetramer. The values for k_4 and k_5 were the largest the program could use. Within wide limits there is no restriction on their magnitude if they are set significantly larger than k_3 and k_5, consistent with there being no detectable concentration of hexameric alkoxide. Further, k_4 and k_5 were arbitrarily set equal; a different ratio would require a corresponding change in the relative values of k_4 and k_3.

This mechanism predicts that, starting from a solution of 0.607 M aluminum isopropoxide (calculated as monomer), the equilibrium concentration of each species at 45° would be, for dimer, 0.077 M; trimer, 0.072 M; tetramer, 0.059 M. These are in reasonably good agreement with the values obtained experimentally: dimer, 0.079 M; trimer, 0.078 M; tetramer, 0.055 M. The mechanism involves assumptions that aluminum isopropoxide does not exist as a monomer, and that it can exist fleetingly as a hexamer. The first of these assumptions was expected, since monomeric aluminum isopropoxide has not been observed; it is dimeric in the vapor phase,[13] even at high temperatures. Since trivalent aluminum is an excellent electron acceptor, and the oxygen of the alkoxide group a good electron donor, it seems likely that it would be at best a transient species with a very high energy barrier to its formation, and consequently playing no part in reactions in solution. The existence of a hexameric form of aluminum isopropoxide has been predicted by Bradley,[3] and, although this form has not been isolated, our mechanism requires its existence only in a very low concentration. It is not even necessary for the hexamer to exist in the structural form predicted by Bradley; a temporary

(13) R. C. Mehrotra, *J. Indian Chem. Soc.*, **31**, 85 (1954).

SCHEME I



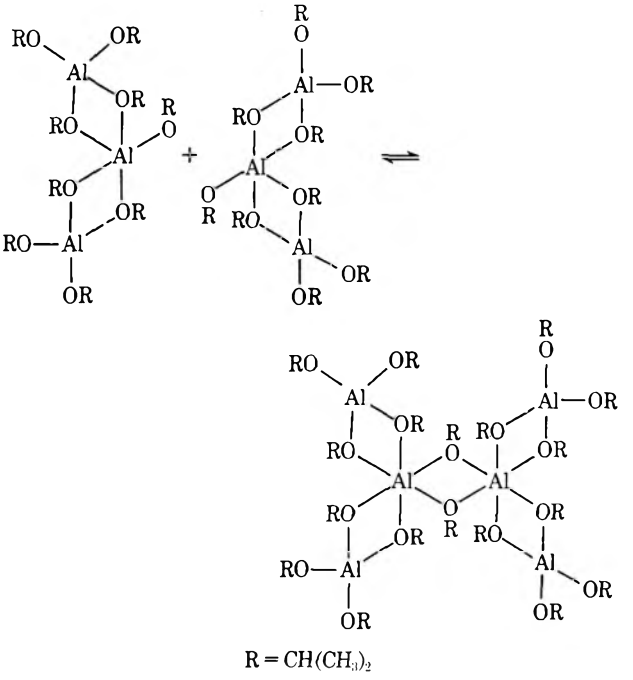
R = $CH(CH_3)_2$

association of the reacting species would satisfy kinetic requirements.

Although the interpretation of our kinetic data described above is not necessarily unique, it provides one possible outline of the sequence of reactions involved in interconversion of the aluminum isopropoxide polymers. It is further consistent with the only information available about any individual step of the reaction, which is the observation that the rate of the tetramer to melt reaction is greatly increased by added alcohol.[12] In benzene at 25°, the formation of melt from tetramer shows first-order kinetic behavior, with $k_1 = 0.11 \times 10^{-6}$ sec^{-1} for an initial concentration of 0.61 *M* alkoxide (measured as monomer). However, repeating the reaction at 25° in a solution containing 0.741 *M* alkoxide (measured as monomer) and 1.274 *M* isopropyl alcohol gave a first-order reaction with $k_1 = 2.5 \times 10^{-6}$, a rate increase by a factor of almost 25. The most probable interpretation of this observation is that the first step of reaction of the tetramer is fission of a bridging aluminum–oxygen bond, the alcohol serving to stabilize the intermediate thus produced, preventing its immediate return to tetramer. This is consistent with observations that the exchange of aluminum isopropoxide and deuterated isopropyl alcohol is zero order in alcohol over the range of concentrations 0.6–2.5 *M*.[12] The alcohol merely serves to block the fast return to tetramer. The requirement that aluminum–oxygen bond fisson in the tetramer is fast and reversible is consistent with the exchange of deuterated acetone with aluminum isopropoxide giving an alkoxide in which all isopropyl groups are equally labeled.[12]

This alkoxy scrambling reaction in the tetramer must involve preliminary aluminum–oxygen bond fisson, as any alternative mechanism would involve formation of 7-coordinate aluminum.[4,12] Taking fission of a bridging aluminum–oxygen bond as the probable first step, then a possible mechanism of the tetramer–dimer interconversion may be written (Scheme I).

The reaction of two molecules of trimer to give a molecule of hexamer almost certainly involves the pentacoordinated aluminum atoms, since these are less stable than the four or six coordinated aluminum atoms, so that a possible mechanism is that shown below.



R = $CH(CH_3)_2$

The loss of the dimeric aluminum isopropoxide unit from the hexamer structure suggested above can be visualized as occurring through a sequence of bonding changes similar to that indicated for loss of a similar unit from the tetramer.

Thus, although there is necessarily a large speculative element in the mechanistic details proposed, and alternative possibilities can be suggested, these mechanisms provide a concise rationalization of the observed structural changes, and involve intermediates containing a minimum of novel structural features.

Acknowledgments.—This investigation was supported by Public Health Service Research Grant No. GM-08502-02 from the National Institutes of Health, Department of Health, Education and Welfare.

Registry No.—Aluminum isopropoxide tetramer, 25443-56-5; aluminum isopropoxide dimer, 32572-47-7; aluminum isopropoxide trimer, 33570-44-4.

Palladium(II)-Catalyzed Exchange and Isomerization Reactions. X. The Acid-Catalyzed Exchange of 2-Cyclohexen-1-yl Esters with Acetic Acid[1]

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Received June 4, 1973

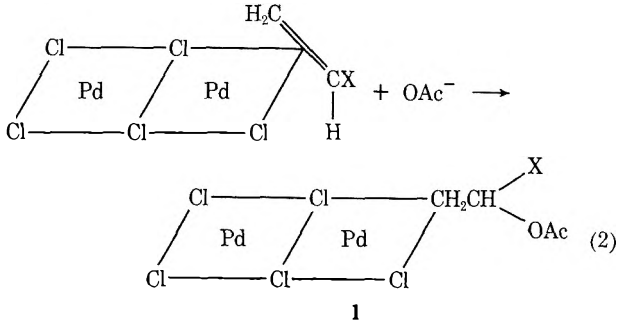
2-Cyclohexen-1-yl propionate does not undergo the acetate ion catalyzed exchange with solvent, the path by which straight-chain allylic propionates react. Instead, this cyclic allylic ester exchanges mainly by an acid-catalyzed reaction whose rate expression is rate = $[Li_2Pd_2Cl_6][2\text{-cyclohexen-1-yl propionate}](k_N + k_A[acid])$ where k_N represents a neutral reaction and k_A the acid-catalyzed reaction. The acid can be acetic acid itself or another stronger acid such as trifluoroacetic. The allylic isomerization of 2-cyclohexen-1-d_1-1-yl acetate-d_3 was one half the rate of exchange of deuterated acetate ester with CH_3COOH solvent. This stereochemical result is consistent with a symmetric intermediate, but not with an acetoxypalladation–deacetoxypalladation type intermediate. The mechanism which appears most consistent with the kinetic and stereochemical results involves a Pd(IV) π-allylic intermediate. A possible reason for the difference in reactivity between 2-cyclohexen-1-yl esters and straight-chain allylic propionates may lie in the conformational energies of the cyclohexene system.

Previous papers in this series have described studies of the Pd(II)-catalyzed exchange of vinylic or allylic esters or chlorides with carboxylate or chloride in solution. It was found that, whenever acetate was the replacing group, the rate expression had the form[3] of eq 1

$$\frac{-d[\text{olefin}]}{dt} = \frac{[Li_2Pd_2Cl_6][\text{olefin}]}{[LiCl]^n}(k' + k''[LiOAc]) \quad (1)$$

(olefin = vinylic or allylic ester or chloride; n = 1 or 2 depending on group being replaced).

This rate expression is consistent with a mechanism involving attack of acetate on a dimeric Pd(II) π complex (X = Cl^- or carboxylate) to give a σ-bonded intermediate (**1**) followed by elimination of X to give exchange.



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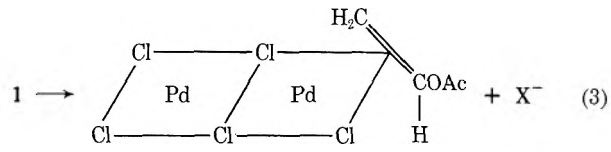


In a study of the exchange of allylic esters with acetate,[3b] an attempt was made to determine the rate of exchange of 2-cyclohexen-1-yl propionate with acetate. At 1 *M* LiOAc the rate of exchange was much slower than would be expected on the basis of steric effects. Furthermore, the rate of exchange was much faster at 0.01 *M* LiOAc. This effect is opposite to that expected on the basis of equation 1 and suggests that 2-cyclohexen-1-yl propionate has a mechanism for exchange which is different from the other allylic esters. This paper will describe a study of this exchange.

Results

All runs were made at 25°. As in previous studies, the concentrations of the various species present in the reaction mixtures were calculated from total Pd(II) ($[Pd(II)]_t$), and chloride ($[Cl]_t$) concentrations using the previously determined[4] values of K_1 (0.1 M^{-1}) and K_D (2.56 M^{-1}) in eq 4 and 5.

$$Li_2Pd_2Cl_6 + 2LiCl \overset{K_1}{\rightleftharpoons} 2Li_2PdCl_4 \quad (4)$$

$$2LiCl \overset{K_D}{\rightleftharpoons} Li_2Cl_2 \quad (5)$$

The earlier qualitative observation[3b] that LiOAc inhibited the rate of exchange was checked by measuring the rate of exchange at constant $[Pd(II)]_t$ and $[Cl]_t$ and various [LiOAc]. The rate did, in fact, decrease with increasing [LiOAc]. This result would be expected if the reaction is acid catalyzed. Thus, since $K_A = [H^+][OAc^-]$, the acid concentration is given by eq 6.[5]

$$[H^+] = K_A/[OAc^-] \quad (6)$$

In turn the acid dependence of rate is given by eq 7.

$$\text{rate} = k[H^+] = kK_A/[OAc^-] \quad (7)$$

Equation 7 predicts that a plot of rate *vs.* $1/[OAc^-]$ should give a straight line if the reaction is acid catalyzed. As shown in Figure 1, such a plot is linear with a positive intercept, indicating a reaction independent of $[H^+]$ as well as a reaction with a first order dependence on $[H^+]$.

To test further the postulate of acid catalysis, runs were made at several CF_3COOH concentrations. As Figure 2 shows, there is a linear increase in rate with increase in $[CF_3COOH]$, confirming the acid catalysis. The positive intercept is the rate at $[CF_3COOH] = 0$ and [LiOAc] = 0 or when $1/[LiOAc] = \infty$. According to Figure 1, the rate should become infinitely rapid at $1/[LiOAc] = \infty$, but of course this is not true since at

(1) Paper IX: P. M. Henry, *J. Org. Chem.*, **38**, 2766 (1973).

(2) (a) University of Guelph. (b) Work by this author carried out at the Hercules Research Center. Address correspondence to this author at the University of Guelph.

(3) (a) P. M. Henry, *J. Amer. Chem. Soc.*, **93**, 3853 (1971); (b) *ibid.*, **94**, 1527 (1972); (c) *ibid.*, **94**, 7311 (1972); (d) *ibid.*, **94**, 7316 (1972).

(4) P. M. Henry and O. Marks, *Inorg. Chem.*, **10**, 373 (1971).

(5) Equation 6 is, of course, a gross oversimplification in that it does not consider ion pairs and the facts that $[H^+]$ exists as H_2OAc^+ and the acetate ion as the biacetate ion $H(OAc)_2^-$. For a discussion of equilibria in acetic acid see ref 6.

(6) A. I. Popov in "The Chemistry of Nonaqueous Solvents, III," J. J. Lagowski, Ed., Academic Press, New York, N. Y., 1970, Chapter 5.

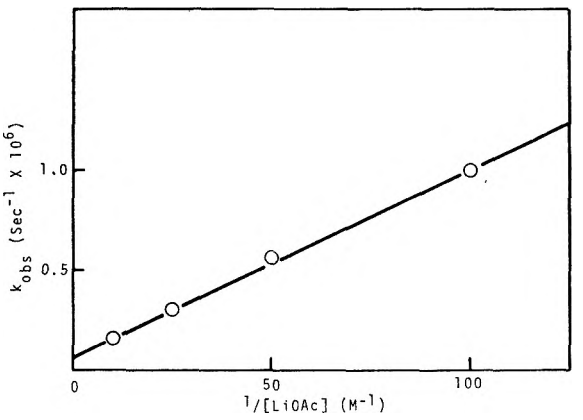


Figure 1.—Plot of k_{obsd} *vs.* 1/[LiOAc]; $[Pd(II)]_t = 0.024\ M$; $[Cl]_t = 0.088\ M$.

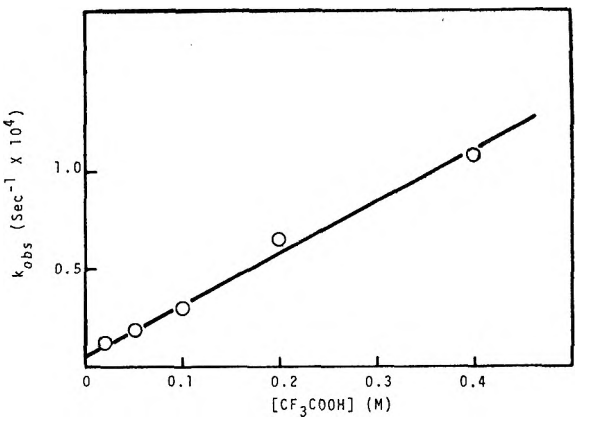


Figure 2.—Plot of k_{obsd} *vs.* $[CF_3COOH]$; $(Pd(II)]_t = 0.024\ M$; $[Cl]_t = 0.088\ M$.

very low added [LiOAc] the concentration of OAc^- is mainly determined by the self-ionization of acetic acid. Next the orders in reactive Pd(II) species and [LiCl] must be determined. Previously it was found that allylic ester exchange[3b] and isomerization[7] were inhibited by the allylic esters themselves because of the following equilibrium to form an unreactive monomeric π complex **2**.

$$Li_2Pd_2Cl_6 + \text{allylic ester} \overset{K_2}{\rightleftharpoons} \underset{\mathbf{2}}{2LiPdCl_3(\text{allylic ester})} \quad (8)$$

The magnitude of this inhibition must be determined, since it will complicate the determination of the order in reactive Pd(II) species. In Table I is shown the effect of allylic ester concentration on rate.

TABLE I

EFFECT OF 2-CYCLOHEXEN-1-YL PROPIONATE CONCENTRATION ON RATE[a]

[2-Cyclohexen-1-yl propionate], M	k_{obsd}, sec^{-1} X 10^5
0.02	3.79
0.10	1.83
0.25	1.60
0.50	0.97

[a] $[Pd(II)]_t = 0.02\ M$ and $[Cl]_t = 0.135\ M$ for all runs.

The dependence of k_{obsd} on allylic ester concentration indicates a value of K_2 in eq 8 of 0.3 M^{-1}. At an allylic ester concentration of 0.02 M or less, the inhibition is negligible. Thus, the Pd(II) dependence was determined using 1-cyclohexen-1-yl propionate concentrations of 0.02 M. As shown in Figure 3, the reaction is strictly first order in $[Li_2Pd_2Cl_6]$.

Finally the order in [LiCl] must be determined. In Table II are listed the values of k_{obsd} for several LiCl concentrations. The value of the ratio in the last column does not change within experimental error; so the reaction is zero order in [LiCl].

The rate expression for the acid region in which LiOAc is added is given by eq 9, in which $[H^+] = K_A/[\text{LiOAc}]$. Using a value of 3.5 X 10^{-15} for K_A,[8] a value of k_2 of 2.6 X 10^6 M^{-2} sec^{-1} can be calculated.

$$\frac{-d[\text{allyl ester}]}{dt} = [Li_2Pd_2Cl_6][\text{allyl ester}](k_1 + k_2[H^+]) \quad (9)$$

(7) P. M. Henry, *J. Amer. Chem. Soc.*, **94**, 5200 (1972).

(8) S. Bruckenstein and I. M. Kolthoff, *J. Amer. Chem. Soc.*, **78**, 2974 (1956).

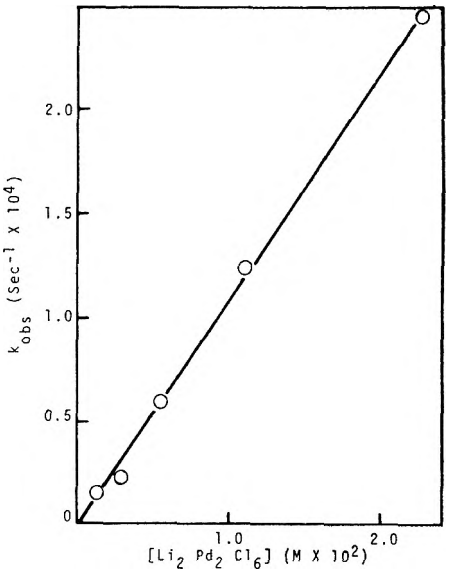


Figure 3.—Plot of k_{obsd} *vs.* $[Li_2Pd_2Cl_6]$; $[CF_3COOH_3] = 0.4\ M$; [2-cyclohexen-1-yl propionate] = 0.02 M; [LiCl] = 0.04–0.06 M.

TABLE II

EFFECT OF LITHIUM CHLORIDE CONCENTRATION ON RATE[a,b]

$[Cl]_t$, M	$[Li_2Pd_2Cl_6]^-$, M X 10^2	[LiCl], M	k_{obsd}, sec^{-1} X 10^5	$\frac{k_{obsd}}{[Li_2Pd_2Cl_6]}$, sec^{-1} M^{-1} X 10^3
0.135	1.120	0.049	1.83	1.63
0.182	1.074	0.077	1.83	1.68
0.276	1.005	0.123	1.51	1.50
0.464	0.908	0.194	1.54	1.70

[a] For all runs $[Pd(II)]_t = 0.024\ M$, $[H^+] = 0.1\ M$, and [allylic ester] = 0.1 M. [b] Values of $[Li_2PdCl_4]$ and $[Li_2Cl_2]$ can readily be calculated from the quantities given in the table.

From the intercept of Figure 1, a value of 4.6 X 10^{-6} M^{-1} sec^{-1} for k_1 can be calculated.

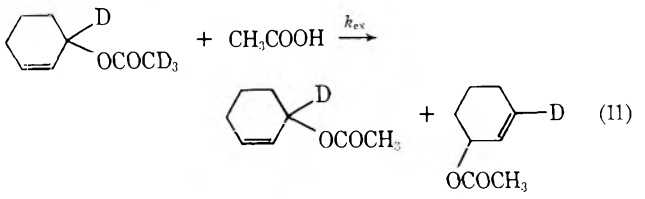
The rate expression for the region in which CF_3COOH is added is given by eq 10.

$$\frac{-d[\text{allyl ester}]}{dt} = [Li_2Pd_2Cl_6][\text{allyl ester}](k_1' + k_2'[CF_3COOH]) \quad (10)$$

The value of k_1' from Figure 2 is 5.8 X 10^{-4} M^{-1} sec^{-1} and the value of k_2' is 2.13 X 10^{-2} M^{-2} sec^{-1}.

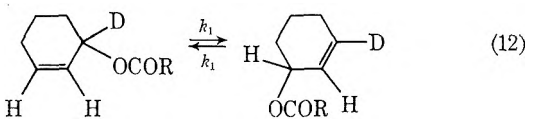
The ratio of exchange to allylic isomerization was determined using 2-cyclohexen-d_1-1-yl acetate-d_3. The

rate of exchange of deuterated acetate was measured by mass spectroscopy. Under one set of reaction con-



(11)

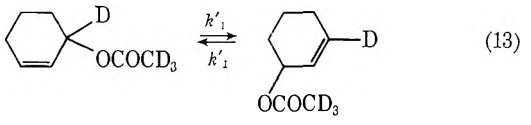
ditions, $[Pd(II)]_t = 0.0218\ M$, $[Cl]_t = 0.0911\ M$, and $[CF_3COOH] = 0.4\ M$, the value of k_{ex} was found to be 1.02×10^{-4} sec^{-1}. The value of exchange for the propionate ester under these conditions is 1.09×10^{-4} sec^{-1}. The rate of allylic isomerization (eq 12, R =



(12)

CH_3 or CD_3) was determined by nmr. Under the same reaction conditions the value of k_i was found to be 5.0×10^{-5} sec^{-1}.

Pd(II) also catalyzes allylic isomerization without exchange[7] (eq 13). If this isomerization were taking



(13)

place it would complicate the interpretation of the stereochemical results for exchange. Now since the value of k_i' does not increase with increasing [LiOAc], the rate of exchange and isomerization at [LiOAc] = 0.02 M was measured. Under these conditions the rate of exchange was 4.5×10^{-7} sec^{-1}, which is about the value expected from the kinetic results with propionate ester. The rate of isomerization was 8.1×10^{-7} sec^{-1} under the same conditions. Since the rate of isomerization is faster than exchange, isomerization without exchange may be important under these conditions. These results are subject to some uncertainty however, because a precipitate of Pd metal was observed after about 2 weeks. The Pd metal may have catalyzed allylic isomerization of the ester. Another possibility is thermal isomerization which is not catalyzed by Pd(II). In any case, at $[CF_3COOH] = 0.4\ M$, the rate of isomerization without exchange would make less than a 2% contribution to the total rate of isomerization.

To determine if straight-chain allylic propionates would undergo the acid-catalyzed exchange, crotyl and 3-buten-2-yl propionate were allowed to react at $[Pd(II)]_t = 0.024\ M$ and $[CF_3COOH] = 0.4\ M$. Exchange was very slow compared with the cyclohexenyl propionates. In fact the esters had isomerized without exchange into an equilibrium mixture before an appreciable exchange occurred.

To establish that the double bond is necessary for exchange, cyclohexyl propionate was exposed to the reaction conditions described above for the crotyl and 3-buten-2-yl propionate. No exchange occurred in several days. Its rate of exchange would be less than $^1/_{1000}$ of the rate for 2-cyclohexen-1-yl propionate.

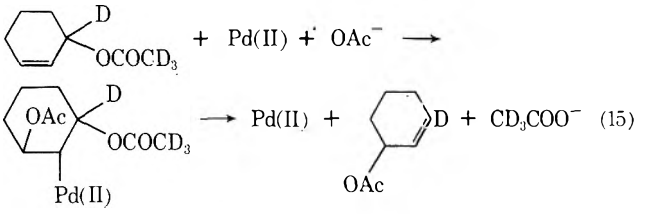
Discussion

Equations 9 and 10 can be summarized in a general rate expression shown in eq 14, where k_N represents the

$$\frac{-d[\text{allyl ester}]}{dt} = ([Li_2Pd_2Cl_6][\text{allyl ester}])(k_N + k_A[\text{acid}]) \quad (14)$$

neutral term which equals k_1 in eq 9 and $k_A[acid]$ is represented by $k_2[H^+]$, k_1', and $k_2'[CF_3COOH]$. Of course the value of k_A depends on the specific acid used.

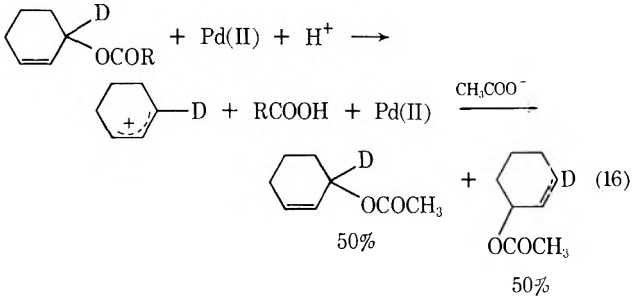
The stereochemical results are not consistent with an acetoxypalladation–deactoxypalladation mechanism proposed for exchange of straight-chain esters[3b,7] because this type of mechanism requires exchange and allylic isomerization to have equal rates. This, of



(15)

course, is not surprising, since the rate expression for this type of mechanism is quite different from that for acid-catalyzed exchange.

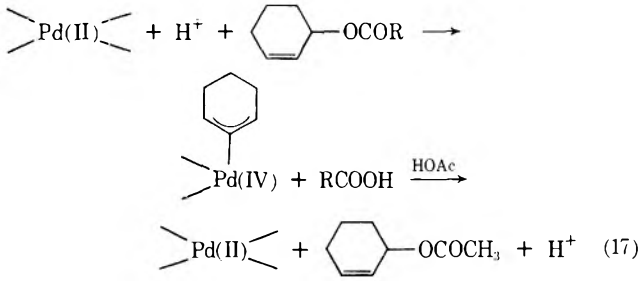
The stereochemical results are, however, consistent with a symmetrical type of intermediate such as an allylic carbonium ion. Since in this case only $^1/_2$ of



(16)

the material is isomerized every time there is exchange, the rate of isomerization is $^1/_2$ the rate of exchange. Although this route is analogous to the postulated mechanism of acid-catalyzed allylic rearrangements carried out in the absence of Pd(II),[9] allylic carbonium ion mechanisms do not have any analogy in other Pd(II) chemistry and the role of the Pd(II) is uncertain.

A mechanism involving a symmetrical intermediate which is more consistent with Pd(II) chemistry involves oxidative addition to Pd(II) to give a Pd(IV) π-allyl. Reversal of this process completes exchange.



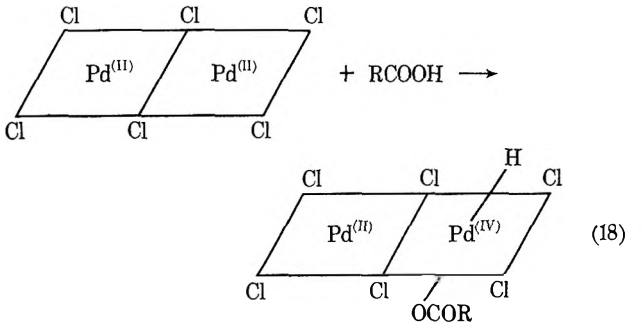
(17)

The ability of d^8 noble metal complexes to form stable d^6 complexes is well known and the role of oxidative

(9) W. G. Young, *J. Chem. Educ.*, **39**, 455 (1962).

addition in catalysis has been discussed.[10-13] Although no stable Pd(IV) π-allyls are known, they have been suggested as intermediates in the Pd(II)-catalyzed double-bond isomerizations.[14,15] Thus there is precedent for proposing Pd(IV) π-allyls as intermediates in Pd(II)-catalyzed reactions.

Presuming a Pd(IV) π-allyl intermediate, the exact mode of formation of this intermediate is uncertain. One path consistent with the rate expression involves oxidative addition of acid (R = CF_3 or CH_3) (eq 18) followed by attack on the allylic ester (eq 19).



(18)

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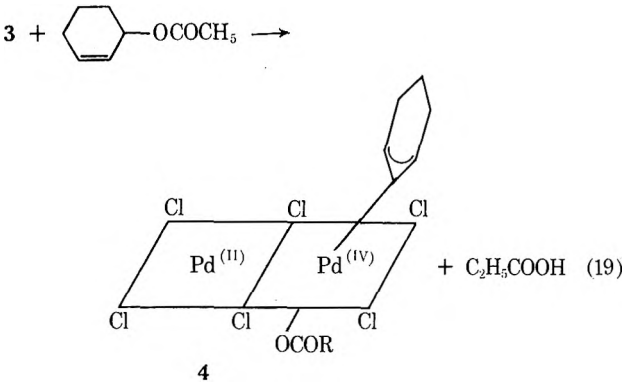

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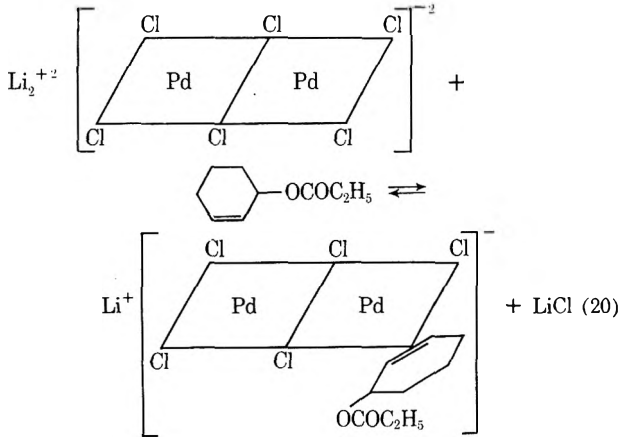
Another route which seems more consistent with Pd(II) chemistry involves initial formation of a dimeric π complex in an initial equilibrium step. Now this



(20)

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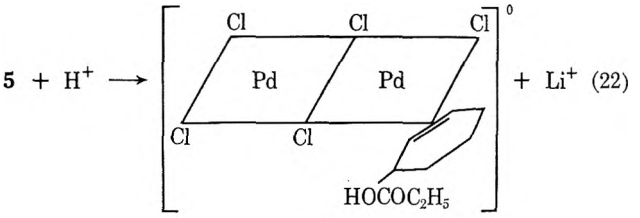
step requires an [LiCl] inhibition term in the denominator of the rate expression which must be cancelled by a term in the numerator to give eq 10. The rate expression would thus be eq 21. Rate expressions in

$$\frac{-\mathrm{d[allyl\ ester]}}{\mathrm{d}t} = \frac{[Li_2Pd_2Cl_6][\text{allyl ester}][LiCl]}{[LiCl]}(k_N + k_A[\text{acid}]) \quad (21)$$

which [LiCl] terms cancelled were proposed for two previous exchanges,[16,17] and, in one case,[16] this assumption was substantiated by further studies.[3c]

The acid catalysis in this path would arise from protonation of the alkyl oxygen of the ester, thus weakening the carbon–oxygen bond. The next step would be oxidative addition to give the Pd(IV) π-allyl. The



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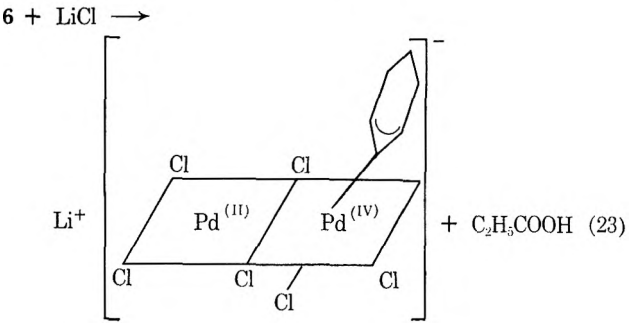


(23)

additional [LiCl] term in the numerator would then be required in this step to fill the sixth coordinative position on the octahedral d^6 Pd(IV).[10,18]

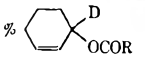
Certainly more work is required to define the exact mechanism with certainty. However, the important point is that a symmetrical intermediate such as a π-allyl complex is required by the stereochemical results.

The present work raises two questions about the special nature of the cyclohexenyl system. First, why does it undergo acid-catalyzed exchange while the straight-chain allylic esters apparently do not? The authors have no explicit answer to the first question but this behavior is consistent with other Pd(II) chemistry of the cyclohexenyl system. Thus, the kinetics of the aqueous oxidation of cyclohexene to cyclohexanone is different from the kinetics of oxidation of straight-chain olefins.[19] This difference may result from a π-allylic type mechanism rather than a hydroxypalladation type mechanism generally accepted for straight-chain olefins.[20] More recently, it has been reported[21,22] that oxidations of cyclohexene in acetic acid apparently occur to a large extent through π-allyl intermediates. Once again, straight-chain olefins are

(10) J. Halpern, *Accounts Chem. Res.*, **3**, 386 (1970).
(11) J. P. Collman, *Accounts Chem. Res.*, **1**, 136 (1968).
(12) R. Cramer, *Accounts Chem. Res.*, **1**, 186 (1968).
(13) L. Vaska, *Accounts Chem. Res.*, **1**, 335 (1968).
(14) J. F. Harrod and A. J. Chalk, *J. Amer. Chem. Soc.*, **88**, 3491 (1966).
(15) N. R. Davies, *Rev. Pure Appl. Chem.*, **17**, 83 (1967).
(16) P. M. Henry, *J. Org. Chem.*, **37**, 2443 (1972).
(17) P. M. Henry, *Inorg. Chem.*, **11**, 1876 (1972).
(18) The π-allyl group is known to occupy two coordination positions.
(19) M. N. Vargaftik, I. I. Moiseev, and Y. K. Sirkin, *Dokl. Akad. Nauk SSSR*, **139**, 1396 (1961).
(20) P. M. Henry, *J. Amer. Chem. Soc.*, **86**, 3246 (1964).
(21) S. Wolfe and P. G. C. Campbell, *J. Amer. Chem. Soc.*, **93**, 1497, 1499 (1971).
(22) R. G. Brown and J. M. Davidson, *J. Chem. Soc. A*, 1321 (1971).

TABLE III

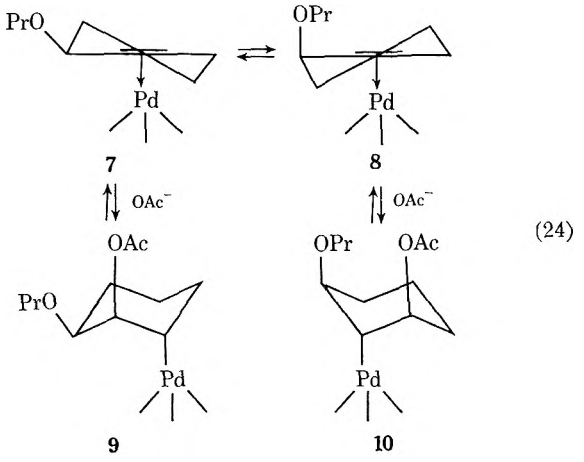
EXCHANGE AND ISOMERIZATION OF 2-CYCLOHEXEN-1-d_1-1-YL ACETATE-d_3[a]

	Exchange		Isomerization	
Time, sec	$\frac{m/e\ 141}{m/e\ 144}$	% acetate-d_3	$\frac{\text{Area HCOCOR}}{\text{area olefinic H}}$	% 
		[CF_3COOH] = 0.4 M		
1,500	0.21	83	0.08	85
3,000	0.35	74	0.11	80
6,000	0.86	54	0.16	72
12,000	2.33	30	0.23	62.5
18,000	5.55	15	0.29	55
		[LiOAc] = 0.02 M		
3.24×10^4	0.07	93.5	0	100
5.62×10^5	0.43	70.0	0.20	67
1.29×10^6	0.92	52.0	0.27	58
2.55×10^7	2.04	32.0	0.32	52

[a] $[Pd(II)]_t = 0.0218\ M$; $[Cl]_t = 0.0911\ M$.

apparently oxidized by an acetoxypalladation type mechanism.[23]

The second question concerns the low reactivity of the cyclohexenyl propionate to the acetate-catalyzed reaction; the answer may lie in the conformational properties of the cyclohexene system. According to the Fürst–Plattner rule,[24] trans attack on cyclohexene oxides[25] and bromonium ions[26] gives diaxially oriented products. The author has recently provided evidence that acetoxypalladation proceeds by a trans attack of acetate on the Pd(II)–cyclohexene π complex.[27] Thus, acetoxypalladation of cyclohexene might also be expected to obey the Fürst–Plattner rule. The scheme for exchange of C_2H_5COO(PrO) with CH_3COO(OAc) is presented in eq 24, where **7** and **8** are the two possible



(24)

conformers of the trans half-chair form π complex. The half-chair is shown because it is much more stable than the half-boat form.[28] The two cis half-chair forms of the π complex are not shown because trans attack on this π complex would not put the OAc^- and Pd(II) in position for the trans elimination required by the principle of microscopic reversibility.

If **7**, which has the propionate in a pseudoequatorial position, is more stable than **8**, the addition of OAc^- to give **9** would be more favorable than addition to give **10**. However, **9** cannot exchange. It can only eliminate OAc^-. If the energy difference between **7** and **8** is large enough, exchange would not be expected by the acetoxypalladation mechanism. Little data is available on the relative stability of 3-substituted cyclohexene derivatives. The pseudoaxial 3-chlorocyclohexene (ΔH = 0.64 kcal/mol) and 3-bromocyclohexene (ΔH = 0.70 kcal/mol) have been reported to be the favored conformers in the pure liquids.[29] Of course, a different order of stabilities could exist for the π complexes **7** and **8**.

Two comments should be made about the rate expressions given by eq 9 and 10. First, in eq 10 the [CF_3COOH] term is to the first power. According to the usual equations for ionization of acids in the absence of buffer, if H^+ (or $H_2{}^+OOCCH_3$) were the catalyst, this term should appear as a $^1/_2$ power term in the rate expression. Since it does not, molecular CF_3COOH must be the catalyst.

Second, if the simple equilibrium shown in eq 6 completely defines the self-ionization of acetic acid, then the value of k_2 in eq 9 can be used to define the value of k_1' in eq 10. According to eq 6, when [LiOAc] = 0, $[H^+] = K_A{}^{1/2}$. Using a value of 3.5×10^{-15} for K_A, we have $[H^+] = 5.9 \times 10^{-8}\ M$. The value of k_1' in eq 10 is then simply $k_2[H^+]$ or $(2.6 \times 10^6\ M^{-2}\ sec^{-1}) \cdot (5.9 \times 10^{-8}\ M)$ or $1.5 \times 10^{-1}\ M^{-1}\ sec^{-1}$. This value for k_1' is considerably higher than the experimental value of $5.8 \times 10^{-4}\ M^{-1}\ sec^{-1}$. The difference reflects the fact that different ion pairs and thus different ion pair dissociation constants are involved in the two systems.[5]

Experimental Section

Materials.—Sources of most chemicals and preparation of stock solutions have been described previously.[3,4] The propionate and acetate esters of 2-cyclohexen-1-ol were prepared by esterification of the alcohol (Aldrich Chemical Co.) using the corresponding anhydride and pyridine as catalyst. Acid catalysts give decomposition of the alcohol. The 2-cyclohexen-1-d_1-1-yl acetate-d_3 was prepared by the reduction of 2-cyclohexenone with $LiAlD_4$ followed by acetylation with $(CD_3CO)_2O$

(23) W. Kitching, Z. Rappoport, S. Winstein, and W. G. Young, *J. Amer. Chem. Soc.*, **88**, 2054 (1966).

(24) A. Fürst and P. A. Plattner, Abstracts of Papers, 12th International Congress of Pure and Applied Chem., New York, N. Y., 1951, p 409.

(25) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 358–360.

(26) Reference 25, p 294.

(27) P. M. Henry and G. A. Ward, *J. Amer. Chem. Soc.*, **93**, 1494 (1971).

(28) Reference 25, p 109.

(29) K. Sakashita, *Nippon Kaguki Zasshi*, **81**, 49 (1960); *Chem. Abstr.*, **54**, 12015*b* (1960).

(Isotopic Products) using the procedure of Campbell.[30] The trifluoroacetic acid was purchased from the Aldrich Chemical Co. It was distilled before use.

Kinetic Runs.—Procedures have been described previously. Runs were usually on a 5-ml scale but runs with 0.02 *M* allyl ester were on a 25-ml scale. Samples were analyzed by vpc using a 6-ft 20% Carbowax 20M on ABS (70–80 mesh) column programmed from 80° to 200° at 7.5°/min. Helium flow rate was 60 ml/min. Runs not containing CF_3COOH were injected without work-up. The runs containing CF_3COOH were neutralized by a 10% excess of 1 *M* LiOAc in HOAc and diluted to a known volume pefore injection. Aliquots (1 or 2 ml) of the 25-ml scale runs were worked up by diluting with CH_2Cl_2 and washing with water to remove HOAc, CF_3COOH, and inorganic salts. After drying over $MgSO_4$, the organic phase was concentrated to a known volume and analyzed by vpc. In one run, the 2-cyclohexen-1-yl acetate was collected by preparative vpc and positively identified by nmr.

2-Cyclohexen-1-d_1-1-yl Acetate-d_3 Run.—A 75-ml reaction mixture which was 0.0218 *M* in Pd(II) and 0.4 *M* in CF_3COOH was prepared and the run was started by adding 1.5 g of the deuterated cyclohexenyl acetate. Samples (12 ml) were worked up by extracting in $CDCl_3$ described above. The samples were analyzed by nmr and mass spectral analysis. The rate of exchange of deuterated ester (eq 11) was determined by the ratio of the parent peaks of the deuterated (*m/e* 144) and undeuterated (*m/e* 141) esters. Data were plotted as a first-order reaction to give k_{ex}. The isomerization rate (eq 12) was determined by nmr using the relative areas of the proton on the carbon containing the acetate[31] and the olefinic protons. Initially this ratio is zero. At equilibrium, when a 50:50 mixture of the two allylic isomers are present, it is 0.33. The data was plotted in the usual fashion for reactions approaching equilibrium. Data[32] are given in Table III.

Acknowledgment.—The authors gratefully acknowledge helpful discussion with Professors H. Georing, S. Wolfe, and H. Taube and Dr. G. Ward. The authors also acknowledge the excellent technical assistance of Mr. F. J. Kriss.

Registry No.—Acetic acid, 64-19-7; 2-cyclohexen-1-yl propionate, 34745-78-3; lithium chloride, 7447-41-8; 2-cyclohexen-1-d_1-1-yl acetate-d_3, 40893-39-8.

(30) P. G. C. Campbell, Ph.D. Thesis, Queen's University, Kingston, Ontario, Canada, 1968, p 256.

(31) See ref 21 for chemical shifts of two types of protons.

(32) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, p 86.

Homogeneous Olefin Hydrogenation Catalyzed by Dichlorodicarbonylbis(triphenylphosphine)ruthenium(II)[1]

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Received March 22, 1973

The relative hydrogenation rates for a variety of alkenes and alkadienes catalyzed by $RuCl_2(CO)_2(PPh_3)_2$ have been measured in the presence of added PPh_3. Rates decrease in the order conjugated dienes > nonconjugated dienes > terminal alkenes > internal alkenes. In general, polyenes are selectively hydrogenated to monoenes. Double bond isomerization and migration reactions and transannular ring closures (in cyclic dienes) can be important competing reactions. The lower hydrogenation rate for alkenes is attributed to an equilibrium between $RuCl(alkyl)(CO)_2$ and $RuCl(alkyl)(CO)_2PPh_3$ intermediates, which, in the presence of added PPh_3, favors the sterically crowded PPh_3 complexed intermediate. Sterically congested intermediates suffer rapid RuH elimination, while the uncongested complexes survive long enough to undergo hydrogenolysis. This equilibrium is not so important for dienes, since the fifth coordination site on ruthenium is already occupied by chelation of the alkenyl ligand.

Numerous catalysts are known that are capable of performing selective homogeneous hydrogenations,[2] but the stabilities and productivities of most of these catalysts have not been well publicized. Thus, despite the alluring appeal many of these catalysts seem to offer in certain applications, their practical value is uncertain. Recently, the selective hydrogenation of 1,5,9-cyclododecatriene to cyclododecene catalyzed by $RuCl_2(CO)_2(PPh_3)_2$ was described.[3] In this case, the catalyst is exceptionally stable under the reaction conditions and is highly productive.[3] Thus, further elaboration of its behavior seems desirable. Herein are provided relative rate data for a variety of unsaturated hydrocarbons that allow a deeper insight into the hydrogenation process.

Results

Selective Hydrogenation of Polyenes.—The presence of added PPh_3 was previously shown to be necessary in order to achieve selective hydrogenations of 1,5,9-cyclododecatriene.[3] Since most of the interest in this catalyst is anticipated to be in its use as a selective hydrogenation catalyst, olefin hydrogenations were routinely performed with added PPh_3. Under these conditions the $RuCl_2(CO)_2(PPh_3)_2$ catalyzed hydrogenations of several diolefins were carried to greater than 99% conversion to yield the product mixtures given in Table I. The data indicate that the selective hydrogenation of polyunsaturated hydrocarbons to monounsaturated hydrocarbons is a fairly general reaction. For 1,5-cyclooctadiene, double bond migration is so rapid that complete isomerization to the 1,3 isomer occurs before significant amounts of cyclooctene appear. Thus, selective hydrogenation of 1,3-cyclooctadiene rather than 1,5-cyclooctadiene was actually observed. Accompanying the double bond migration reaction in 1,5-cyclooctadiene is a cyclization to bicyclo[3.3.0]oct-2-ene. This by-product was formed in 0.4% yield as 1,5-cyclooctadiene was undergoing

(1) Presented in part at the 19th Oklahoma American Chemical Society Tetrasectional Meeting, Bartlesville, Okla., Mar 10, 1973.

(2) For recent comprehensive reviews, see: (a) J. E. Lyons, L. E. Rennick, and J. L. Burmeister, *Ind. Eng. Chem. Prod. Res. Develop.*, **9**, 2 (1970); (b) A. Andreeta, F. Conti, and G. F. Ferrari in "Aspects of Homogeneous Catalysis," Vol. I, R. Ugo, Ed., Carlo Manfredi Editore, Milano, 1970, Chapter 4.

(3) D. R. Fahey, *J. Org. Chem.*, **38**, 80 (1973).

TABLE I

SELECTIVITY OF POLYENE TO MONOENE HYDROGENATION AT >99% POLYENE CONVERSION[a]

Polyene	Registry no.	PPh_3, M	$RuCl_2(CO)_2(PPh_3)_2$, M	Reaction time, hr	Yield, % Polyenes	Alkenes	Alkanes	Selectivity[b]
1,3-Pentadiene	504-60-9	0.0356	0.00031	0.5	0.0	99.3	0.7	0.99
1,5,9-Cyclododecatriene	4904-61-4	0.0356	0.00247	12.9	0.6	97.3	1.9	0.98
1,5-Cyclooctadiene	111-78-4	0.078	0.00314	3.2	0.8	93.4[c]	6.1	0.94
Norbornadiene	121-46-0	0.078	0.00314	1.0[d]	0.4	80.2	19.4[e]	0.81
3,3-Dimethyl-1,4-pentadiene	1112-35-2	0.078	0.00154	6.0	0.3	37.5	62.3	0.37[f]

[a] Reactions were performed in benzene solutions at ~140° under 150–200 psig. Polyene concentrations were 0.25–0.59 M. [b] Selectivity = [alkene]/([alkene] + [alkane]). [c] Alkenes are cyclooctene (93.0%) and bicyclo[3.3.0]oct-2-ene (0.4%). [d] Nearly all the hydrogen absorption occurred in the first 10 min, but the reaction conditions were maintained for 1.0 hr. [e] Alkanes are norbornane (2.4%) and nortricyclene (17.0%). [f] At 99.0% conversion, the selectivity is estimated to be 0.51 to 0.53.

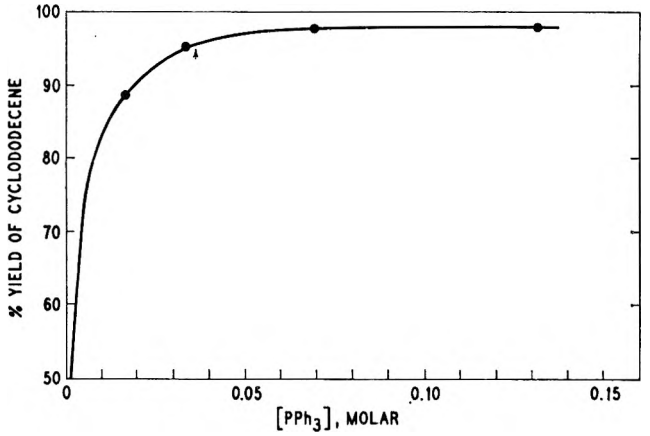


Figure 1.—Effect of added PPh_3 concentration on the maximum yield of cyclododecene attainable in the hydrogenation of 1,5,9-cyclododecatriene (0.55 M) catalyzed by 0.006 M $RuCl_2(CO)_2(PPh_3)_2$. The arrow is located at 0.0356 M PPh_3. Plotted from data given in ref 3.

isomerization. After 1,5-cyclooctadiene had disappeared, the concentration of the bicyclic compound remained constant. No bicyclo[3.3.0]octane was detected during the hydrogenation. A cyclization also occurred during the hydrogenation of norbornadiene as nortricyclene was formed in 17% yield. If this by-product were neglected, the selectivity value for norbornadiene in Table I would be 0.97 rather than 0.81. For the other olefins, the hydrogenation products were normal. The hydrogenation of 1,3-pentadiene produced pentene with a 1-ene/*cis*-2-ene/*trans*-2-ene isomer ratio of 4:25:70 which remained constant. This same ratio of isomers is rapidly formed from 1-pentene under the hydrogenation conditions.[4]

Rate Studies.—All hydrogenation rates were determined at 140° in benzene with 0.0356 M PPh_3 under a total pressure of 200 psig. This concentration of PPh_3 was somewhat arbitrarily chosen and is approximately the minimum necessary to achieve a highly selective hydrogenation of 1,5,9-cyclododecatriene, as illustrated in Figure 1. Since the pressure in the system is derived from the partial pressures of benzene, the olefin, and hydrogen, the partial pressure of hydrogen was not maintained constant for all olefins studied. If hydrogenations are first order in hydrogen (this is believed to be true) and if the solutions obey Raoult's law, the rate constants for the olefins in Table II, except 1,3-pentadiene and the pentenes, are influenced less than 2%. For 1,3-pentadiene and the pentenes, the rate constants in Table II are 7% low. It was

TABLE II

SECOND-ORDER RATE CONSTANTS FOR THE HYDROGENATION OF UNSATURATED HYDROCARBONS BY $RuCl_2(CO)_2(PPh_3)_2$[a]

Registry no.	Unsaturated hydrocarbon	K[b]
	1,3-Pentadiene	14,000
	3,3-Dimethyl-1,4-pentadiene	224
	Cyclododecadienes[c]	66
40999-81-3	1,3	
40999-82-4	1,4	
1502-04-1	1,5	
20006-42-2	1,6	
7158-18-1	1,7	
	1,5,9-Cyclododecatriene[c]	43
100-42-5	Styrene	29
3404-73-7	3,3-Dimethyl-1-pentene	27
	Pentenes	7.1
109-67-1	-1-ene	
627-20-3	-*cis*-2-ene	
646-04-8	-*trans*-2-ene	
1501-82-2	Cyclododecene[c]	0.6

[a] Reaction rates were determined at 140° and 200 psig in benzene solutions containing 0.31–3.1 × 10^{-3} M $RuCl_2(CO)_2(PPh_3)_2$, 0.0356 M PPh_3, and 0.25–0.59 M olefin. Rate constants presumably contain terms for hydrogen and PPh_3 concentrations. [b] Units of mol^{-1} l. sec^{-1} × 10^3. [c] Rate constant values were taken from ref 3.

necessary to use varied concentrations of $RuCl_2(CO)_2(PPh_3)_2$ to ensure conveniently measurable rates or to prevent a diffusion-controlled reaction as dictated by the activity of the olefin. Hydrogenation rates were previously shown to be linearly dependent on the concentration of $RuCl_2(CO)_2(PPh_3)_2$.[3]

Rate constants were calculated using the relationship shown in eq 1, where [Ru] is the concentration

$$-d[\text{olefin}]/dt = K[\text{Ru}][\text{olefin}] \quad (1)$$

of $RuCl_2(CO)_2(PPh_3)_2$ and the apparent rate constant K presumably contains terms for PPh_3 and hydrogen concentrations. For all olefins, plots of ln [olefin]/[olefin]$_0$ *vs.* time were linear. For the consecutive hydrogenation of 3,3-dimethyl-1,4-pentadiene to 3,3-dimethyl-1-pentene to 3,3-dimethylpentane, the rate constant for diene hydrogenation was obtained with eq

(4) This ratio is therefore presumed to be the thermodynamic equilibrium ratio at 140°. The experimentally determined equilibrium ratio at 25° is 1.5:17.5:81 [G. C. Bond and M. Hellier, *Chem. Ind. (London)*, 35 (1965)]. Very different ratios (9:41:51 at 140° and 3:32:65 at 25°) are obtained from the free energy of formation values given in F. D. Rossini, "Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds," Carnegie Press, Pittsburgh, Pa., 1953, p 737.

1, but the rate constant for alkene hydrogenation was determined using eq 2 at the point where the alkene

$$K_{alkene} = K_{diene}\,[diene]/[alkene] \text{ at } [alkene]_{max} \quad (2)$$

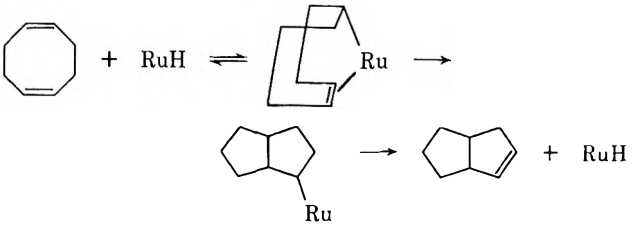
attained its maximum concentration during the hydrogenation. The derivation of eq 2 was given previously.[3] Hydrogenation rates for a variety of unsaturated hydrocarbons are listed in Table II.

Discussion

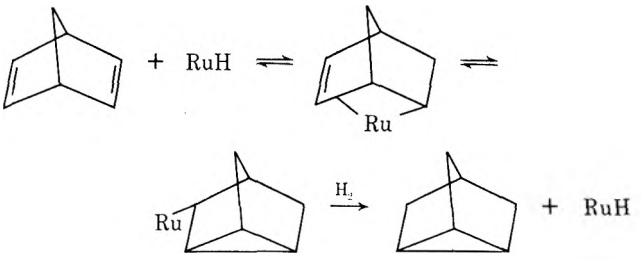
From the results of the present work and those from the previous[3] study, several general comments can be made about $RuCl_2(CO)_2(PPh_3)_2$ catalyzed hydrogenations.

1.—Hydrogenation rates decrease in the order conjugated dienes > nonconjugated terminal dienes > nonconjugated internal dienes > terminal alkenes > internal alkenes. The order of rates parallel the relative stabilities of π-bonded Ru–olefin intermediates towards olefin dissociation and also the predicted relative stabilities of the alkyl–ruthenium intermediates derived from these olefins towards RuH elimination. Ruthenium(II) complexes of dienes are stable,[5-7] but no Ru(II) complexes with simple alkenes have been isolated.[6] The stabilities of the alkyl–ruthenium intermediates would be predicted to decrease in the order π-allyl complexes (formed from conjugated dienes) > σ,π-chelated complexes (from nonconjugated dienes) > *n*-alkyl complexes (from terminal alkenes) > *sec*-alkyl complexes (from internal alkenes). The hydrogenation of 1,3-pentadiene is extremely rapid, and a π-allyl intermediate is undoubtedly formed. The apparent low hydrogenation rates for the C_{12} polyenes in Table II is attributed to the reluctance of the double bonds to migrate into conjugation. The only positional isomer of cyclododecatriene known is the 1,5,9 isomer.[8] The most stable cyclododecadiene isomers are also nonconjugated, and the equilibrium isomer mixture at 200° has been found to be 1,3- (10%), 1,4- (6%), 1,5- (57%), 1,6- (16%), and 1,7- (11%).[9] 3,3-Dimethyl-1,4-pentadiene is a nonconjugated diene but is hydrogenated more rapidly than the C_{12} polyenes since terminal alkenes are hydrogenated faster than internal alkenes. Low rates for the hydrogenation of nonterminal alkenes using $RuClH(PPh_3)_3$ and $RuH(OCOCF_3)(PPh_3)_3$ complexes have been attributed to a difficulty in hydride transfer to coordinated alkene as a result of steric interaction with the PPh_3 groups.[7,10,11] This steric interaction induces a strong preference for anti-Markovnikov addition of RuH to terminal alkenes leading to a less sterically congested primary carbon–ruthenium σ bond.[7] 3,3-Dimethyl-1,4-pentadiene is hydrogenated seven times faster than 3,3-dimethyl-1-pentene. The rate enhancement over a statistical factor of 2 must result from an ability of the diene to chelate with ruthenium. The relative order of alkene hydrogenation rates is consistent with the above discussion as terminal alkenes are hydrogenated more rapidly than nonterminal alkenes, and the mixture of pentene isomers is hydrogenated at a sensibly intermediate rate.

2.—Dienes indeed form chelated complexes. Side reactions occurring during the hydrogenations of 1,5-cyclooctadiene and norbornadiene are best explained by the intervention of σ,π-chelated intermediates. The 0.4% yield of bicyclo[3.3.0]oct-2-ene from 1,5-cyclooctadiene thus arises by intramolecular insertion of a coordinated C=C bond into a Ru–C bond as shown.



Likewise, the formation of nortricyclene from norbornadiene undoubtedly results from intermediates of the type shown below. Both norborn-π,5-en-2-yl



and nortricyc-3-lyl complexes of palladium are known,[12-14] and, under certain circumstances, the σ,π-chelated complex could be rearranged to the nortricyclyl complex.[12] A proposal[12,15] that the norborn-π,5-en-2-yl complex may be more accurately depicted as a π-homoallylic system is also very attractive here, since both norbornene and nortricyclene could be produced from a common intermediate. In addition, the rate of norbornadiene hydrogenation qualitatively compares with that of 1,3-pentadiene.

3.—Isomerization is usually faster than hydrogenation. Cyclododecene is hydrogenated the slowest of all the olefins in Table II; yet its rate of cis to trans isomerization (k = 0.54 mol^{-1} l. sec^{-1})[3] is several hundred times faster than its hydrogenation and is even considerably faster than the hydrogenations of the other olefins in Table II excepting 1,3-pentadiene. Similarly, 1,5-cyclooctadiene is isomerized very rapidly to 1,3-cyclooctadiene which is then more slowly hydrogenated. Thus, for at least the nonconjugated olefins, the rate of RuH addition to the olefin and its reverse are much faster than hydrogenation. For 1,3-pentadiene, the trans/cis ratio increased from 2.0 initially to 4.0 at 98% conversion. In this case, isomerization is not sufficiently rapid to maintain the trans/cis ratio constant at the equilibrium value.

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(6) S. D. Robinson and G. Wilkinson, *J. Chem. Soc. A*, 300 (1966).
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(10) D. Rose, J. O. Gilbert, R. P. Richardson, and G. Wilkinson, *J. Chem. Soc. A*, 2610 (1969).
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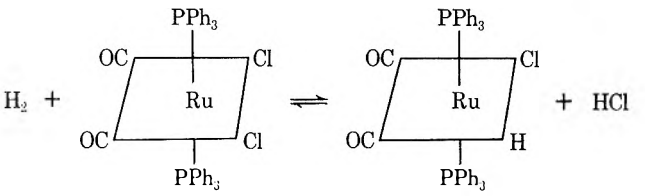
(13) J. K. Stille and L. F. Hines, *ibid.*, **92**, 1798 (1970).
(14) E. Vedejs and M. F. Salomon, *ibid.*, **92**, 6965 (1970).
(15) M. Green and R. I. Hancock, *J. Chem. Soc. A*, 2054 (1967).

This is in agreement with a high stability of π-allyl complexes towards reversion to RuH and diene. Since the same initial steps are involved in both hydrogenation and isomerization, *i.e.*, formation of an alkyl–ruthenium intermediate, the rate-controlling step for hydrogenation must come after the formation of this intermediate. For conjugated dienes, there is no direct evidence for the validity of this conclusion, but this must certainly be true since RuH addition to 1,3-pentadiene should be very much faster than to *cis*-cyclododecene while hydrogenation of 1,3-pentadiene is only 2.6 times faster than isomerization of *cis*-cyclododecene. In hydrogenations catalyzed by the closely related $RuClH(PPh_3)_3$ and $RuH(OCOCF_3)(PPh_3)_3$ complexes, the kinetics agree with the rate-determining step being attack of hydrogen on an alkyl–ruthenium intermediate.[11]

4.—Added PPh_3 slows hydrogenations. The presence of added PPh_3 (0.0356 *M*) slows cyclododecene hydrogenation by a factor of 74, but cyclododecatriene and cyclododecadiene hydrogenations are slowed only by a factor of 2 to 3.[3] The lower sensitivity of polyene hydrogenation rates to added PPh_3 can be accounted for in terms of steric factors, exerted by coordinated PPh_3, that are more important for alkenes than for dienes. Dienes, unlike alkenes, can occupy an additional site on the catalyst, *via* chelation, which would otherwise be occupied by PPh_3. Added PPh_3 severely inhibits the hydrogenation activities of $RuClH(PPh_3)_3$ and $RuH(OCOCF_3)(PPh_3)_3$, but for a different reason.[7,10,11] For these complexes PPh_3 dissociation is suppressed.[7,10,11] This type of phenomenon seems less important in the hydrogenations using $RuCl_2(CO)_2(PPh_3)_2$.

Nature of Catalyst.—Since the ruthenium complex $RuCl_2(CO)_2(PPh_3)_2$ can be recovered from reaction mixtures after hydrogenations are completed,[3] it satisfies the formal definition of a catalyst. However, additional complexes, that are in equilibrium with $RuCl_2(CO)_2(PPh_3)_2$, may participate in the hydrogenation process. Data presented in the results section of the earlier paper, but not discussed, rules out $Ru(H)_2(CO)_2(PPh_3)_2$ as a likely intermediate. This complex was prepared *in situ* by known reactions [$RuCl_2(CO)_2(PPh_3)_2 + LiAlH_4$[16] and $Ru(CO)_3(PPh_3)_2 + H_2$[17]], and it performed differently in the hydrogenation of 1,5,9-cyclododecatriene than did $RuCl_2(CO)_2(PPh_3)_2$.[3] Another strong possibility for an intermediate could be $RuClH(CO)(PPh_3)_3$, since this type of complex can be formed from $RuClH(CO)_2(PPh_3)_2$ and PPh_3 at high temperatures.[18] However, the hydrogenation of 1,5,9-cyclododecatriene catalyzed by $RuClH(CO)(PPh_3)_3$ (prepared *in situ* from $RuCl_3$, CO, H_2, and PPh_3 and isolated after completion of the hydrogenation) was less selective than with $RuCl_2(CO)_2(PPh_3)_2$.[19] An intermediate with the composition $RuClH(CO)_2(PPh_3)_2$ seems to be most reasonable. Similar to the formation of $RuClH(PPh_3)_3$ from $RuCl_2(PPh_3)_3$,[7,11] conversion of $RuCl_2(CO)_2(PPh_3)_2$ to $RuClH(CO)_2(PPh_3)_2$, which is shown below, is facilitated by bases such as PPh_3.[3]



The first step in hydrogenations catalyzed by $RuClH(PPh_3)_3$ and $RuH(OCOCF_3)(PPh_3)_3$ is proposed to be a PPh_3 dissociation from the catalyst.[7,10,11] This is supported by inhibition by added PPh_3 and by a molecular weight determination of $RuH(OCOCF_3)(PPh_3)_3$. Molecular weight determinations for $RuCl_2(CO)_2(PPh_3)_2$ have however indicated little or no PPh_3 dissociation.[3,20] Yet dissociation of PPh_3 from the catalyst must be extensive at 140° since diene hydrogenations are retarded only slightly by the mass action effect of added PPh_3. Likely, PPh_3 dissociation is induced by thermal stimulation. The presence of interligand spin–spin nuclear coupling involving ^{31}P nuclei, *e.g.*, **P**–Ru–**H** coupling in the ^1H nmr spectrum of $Ru(H)_2(CO)_2(PEt_3)_2$[16] and **P**–Ru–**P** coupling in the ^{13}C nmr spectrum of $RuCl_2(CO)_2(PPh_3)_2$,[3] has not proved to be a reliable probe in the assessment of PPh_3 dissociation. The $RuH(OCOCF_3)(PPh_3)_3$ complex, which is known to dissociate in solution, still exhibits a quartet hydride resonance in its ^1H nmr spectrum due to P–H coupling.[10]

Origin of Selectivity and Reaction Mechanism.—Any mechanistic proposals must account for the large hydrogenation rate decrease experienced by internal alkenes compared to polyenes when PPh_3 is added; yet alkene isomerization remains rapid. The mechanism of olefin hydrogenations catalyzed by the closely related $RuClH(PPh_3)_3$[7,11] and $RuH(OCOCF_3)(PPh_3)_3$[10] complexes has previously been elucidated. In its published form,[11] the mechanism does not adequately explain the results with the dicarbonyl catalyst. However, it becomes applicable with the incorporation of additional intermediates and equilibria as shown in Scheme I. Initially, the $RuClH(CO)_2(PPh_3)_2$ species is formed in step 1 as discussed in the preceding section. Dissociation of PPh_3 from $RuClH(CO)_2(PPh_3)_2$ occurs in step 2; so this step should be subject to a mass action effect of added PPh_3. If the sole function of added PPh_3 in slowing the hydrogenation of 1,5,9-cyclododecatriene (the C_{12} olefin least affected by added PPh_3) is to suppress this dissociation step, then a reasonable estimate for K_2 is 0.03 to 0.04 mol $l.^{-1}$. Next, the olefin coordinates to the catalyst and is followed by RuH addition to the coordinated olefin *via* steps 3, 8, and 12. These steps must be rapid for all alkenes and more rapid for dienes. The equilibrium constant K_8 is predicted to be large due to the high trans labilizing effect of an alkene in ligand substitution reactions.[21] The forward direction of step 4 would not be a favorable reaction since the bulky PPh_3 group is expected to hinder hydride transfer to the coordinated alkene.[11] Hydrogenation then proceeds through steps 13 and 14, where (13) is presumably the rate-controlling step in the overall scheme.

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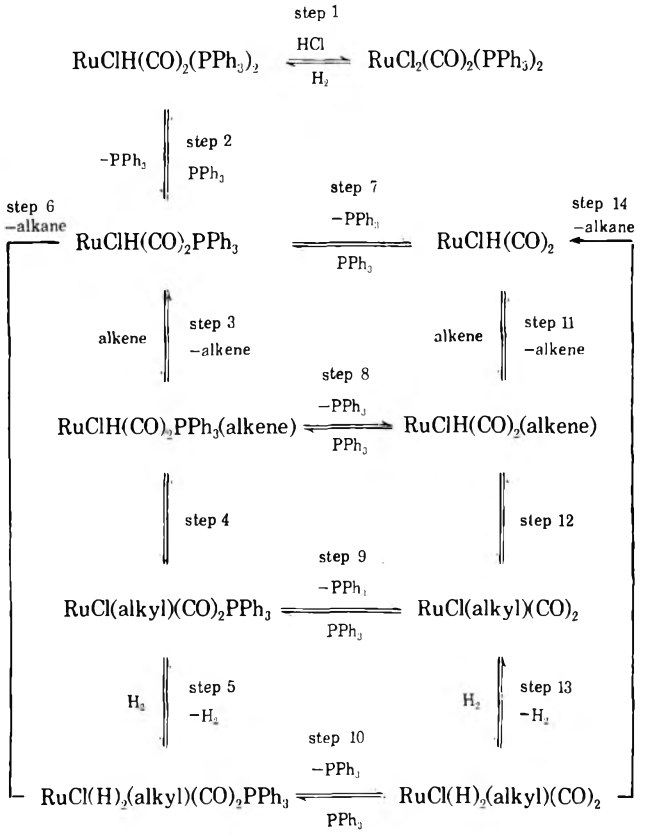
SCHEME I



Hydrogen activation step 5, like (13) is also rate determining and might be expected to be slower than (13) on steric grounds, since a seven-coordinate intermediate is involved. Rate differences between alkenes and dienes emerge in the sensitivity of equilibrium 9 to PPh_3 concentration. In alkene hydrogenations, added PPh_3 shifts equilibrium 9 in the direction of the $RuCl(alkyl)(CO)_2PPh_3$ complex. The complexed PPh_3 group increases the steric congestion about ruthenium, especially for *sec*-alkyl–ruthenium intermediates, and a RuH elimination occurs *via* the reverse direction of step 4. In diene hydrogenations, equilibrium 9 is not so important since the reactive coordination site on ruthenium is already occupied by the pendent C=C of the alkenyl ligand.

The four-coordinate ruthenium(II) intermediates in Scheme I appear to violate the 16 and 18 electron rule promulgated by Tolman.[22] This objection can be reconciled by allowing other olefins or the benzene solvent to coordinate weakly to these intermediates. In the hydrogenation of 1,5,9-cyclododecatriene, coordination by benzene is indicated by the higher selectivity to cyclododecene in benzene than in either 1-butanol or ethyl acetate.[3] Benzene complexes of ruthenium(II) are known.[23,24] Four-coordinate alkyl–ruthenium(II) complexes are favored by Wilkinson and his coworkers[7,10] as intermediates in their hydrogenation mechanisms, since they lead to octahedral $Ru(H)_2(alkyl)X(PPh_3)_2$ complexes in the hydrogen activation step. However, there is also precedent for the addition of hydrogen to five-coordinate ruthenium(II) complexes, as in step 5 of Scheme I, in the reaction of hydrogen with $Ru(H)_2(PPh_3)_3$ to form $Ru(H)_4(PPh_3)_3$.[25,26] A number of reaction paths other than those described in Scheme I have been considered but they do not seem to explain adequately the behavior of the catalyst without resorting to seven-coordinate ruthenium(II) intermediates (20-electron complexes).

The relative hydrogenation rates of dienes *vs.* alkenes catalyzed by $RuCl_2(CO)_2(PPh_3)_2$ are opposite to those of hydrogenations catalyzed by $RuClH(PPh_3)_3$[7] and $RuH(OCOCF_3)(PPh_3)_3$.[10] These differences can be rationalized by a greater steric hindrance in the addition of hydrogen to five-coordinate Ru(alkenyl)-$X(PPh_3)_2$ complexes as compared to four-coordinate $Ru(alkyl)X(PPh_3)_2$ complexes. By replacing the bulky PPh_3 ligands with the smaller CO groups, this steric hindrance is relieved, and the addition of hydrogen to five-coordinate $RuCl(alkenyl)(CO)_2$ complexes is sterically allowed. An additional consequence of electron-withdrawing CO ligands is that the "promotional energy"[27] required in the hydrogen activation steps is increased compared to the other ruthenium catalysts; thus more vigorous conditions are required for the dicarbonyl complex to function as a catalyst.

Experimental Section

Reagents.—Olefins, except 3,3-dimethyl-1,4-pentadiene which was donated by P. W. Solomon, were purchased in high purity from commercial sources. All were passed through activated alumina immediately before use. Benzene was purified by distillation from CaH_2, and triphenylphosphine was recrystallized from ethanol. *cis*-Dichloro-*cis*-dicarbonyl-*trans*-bis(triphenylphosphine)ruthenium(II)[3] was synthesized by the procedure of Stephenson and Wilkinson.[20] As in the earlier work,[3] the complex was purified by filtering its CH_2Cl_2 solution through activated alumina followed by several recrystallizations from CH_2Cl_2–CH_3OH solutions. Despite these measures, reaction rates were not always reproducible from one sample preparation to another. Therefore, the relative rates in Table II were all measured using $RuCl_2(CO)_2(PPh_3)_2$ from a single sample preparation.

Hydrogenations.—The apparatus and technique used in the rate studies were described previously.[3] Liquids were transferred to the hydrogenation apparatus with a minimum of exposure to air, and the apparatus was immediately flushed with hydrogen to remove air. Although the presence of air or hydroperoxides does influence olefin isomerization reactions catalyzed by $RuCl_2(PPh_3)_3$ by converting the complex into a carbonyl complex,[28] a similar interference is not anticipated here, since, if a tricarbonylruthenium(II) complex were formed, it would be expected to revert to a dicarbonyl complex in the presence of PPh_3.[29] Further, atmospheric oxygen was earlier shown to oxidize PPh_3 to $OPPh_3$ in the present system.[3] A constant 200 psig pressure was maintained in all rate studies, and the bath temperature was 140 ± 0.4°.

Product Identification and Analysis.—Reaction samples were analyzed by glpc on a Hewlett-Packard Model 5750 instrument equipped with a 20 ft × 0.25 in. column packed with 20% tris-1,2,3-(2-cyanoethoxy)propane on 60–80 Chrom P. A flame ionization detector was used. Product identities were determined by comparison of their glpc retention times with those of authentic

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(29) M. I. Bruce and F. G. A. Stone, *J. Chem. Soc. A*, 1238 (1967).

samples, except for 1,4-cyclooctadiene and 3,3-dimethyl-1-pentene. The former was assumed to be the intermediate product in the isomerization of 1,5-cyclooctadiene to 1,3-cyclooctadiene, while the latter was assumed to be the intermediate in the hydrogenation of 3,3-dimethyl-1,4-pentadiene to 3,3-dimethylpentane. Authentic nortricyclene was obtained by treating a solution of the Grignard reagent of 3-bromonortricyclene[30] with anhydrous HCl. Bicyclo[3.3.0]oct-2-ene was a gift from Dr. P. R. Stapp.

Registry No.—$RuCl_2(CO)_2(PPh_3)_2$, 29079-66-1.

(30) Purchased from Aldrich Chemical Co.

The Role of Hydrate Formation in the Chromium(VI) Oxidation of Aldehydes[1]

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Received April 30, 1973

Reaction rates for the chromic acid oxidation of a series of aliphatic aldehydes have been determined and correlated with aldehyde hydration equilibria. A value of $\rho^* = -1.1$ for the oxidation of aldehyde hydrates has been obtained. The results support a mechanism consisting of a rate-limiting oxidative decomposition of a chromic acid ester of an aldehyde hydrate. The applicability of the mechanism to the oxidation of aromatic aldehydes is discussed. The deuterium isotope effect for the oxidation of pivaldehyde ($k_H/k_D = 7.9$) shows that even this aldehyde reacts "normally" by carbon–hydrogen rather than by a carbon–carbon cleavage.

We have earlier pointed out that the chromium(VI) oxidation of aldehydes can be better understood and correlated with the oxidation of alcohols if it is regarded as an oxidation of an aldehyde hydrate rather than of the free carbonyl compound.[2,3]

In the course of the investigation of the chromium(IV) oxidation of aldehydes[4] we needed to determine the chromium(VI) oxidation of a larger series of aliphatic aldehydes. Since a great deal more information on aldehyde hydration equilibria is now available,[5-11] we were able to analyze the data more completely than could be done at the time of our earlier investigation.[2]

Table I summarizes the experimental rate constants, k_{obsd}, for the chromic acid oxidation of a series of eight aliphatic aldehydes. Also given are the aldehyde hydrate dissociation constants, K_d, pertaining to the reaction $RCH(OH)_2 \rightleftarrows RCHO + H_2O$. From k_{obsd} and K_d, two sets of rate constants referring to the oxidation of the aldehyde in only one of the forms present in solution were computed. The values for k_H were obtained by assuming that only the hydrated form will appear in the rate law

$$v = k_H[Cr(VI)][RCH(OH)_2] \quad (1)$$

Conversely, the value for k_A was calculated using only the concentration of the free aldehyde according to the rate law[12]

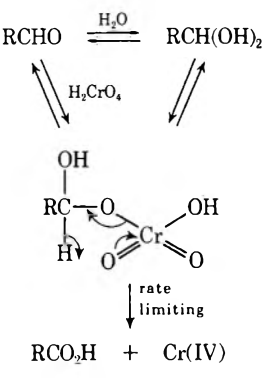
$$v = k_P[Cr(VI)][RCHO] \quad (2)$$

A plot of log k_H against Taft's substituent constants σ^* gives a good straight line (Figure 1; correlation coefficient 0.99, standard deviation 0.2) with a slope of $\rho^* = -1.1$.[13] On the other hand, the correlation of σ^* with k_A is much less satisfactory. The main deviation is observed for formaldehyde, which appears to be almost 1000 times more reactive than would be predicted from the $\sigma^*\rho^*$ plot based on the other aldehydes. When the value for formaldehyde is ignored, a straight line (correlation coefficient 0.97, standard deviation 0.16) giving a value of $\rho^* = 0.53$ may be obtained.

In the above results, the case of formaldehyde is of particular interest. If one assumes that the aldehyde reacts *via* the hydrate (eq 1), a rate constant, k_H, is obtained which compares well with the reactivities of other aldehydes. On the other hand, if only free formaldehyde could be oxidized, then one would have to assume that formaldehyde is about 1000 times more reactive than other aldehydes. This makes a mechanism consisting of a direct hydrogen transfer reaction between the free aldehyde and chromic acid (to yield, *e.g.*, $R\dot{C}{=}O$ or $RC^+{=}O$) very unlikely.

The results obtained in this study thus agree well with the mechanism in which the rate-limiting step is the oxidative decomposition of a chromic acid ester of an aldehyde hydrate (Scheme I).

SCHEME I



(1) The support of this work by the National Science Foundation is gratefully acknowledged.

(2) J. Roček, *Tetrahedron Lett.*, **No. 5**, 1 (1959).

(3) For a more detailed discussion, *cf.* J. Roček in "The Chemistry of the Carbonyl Group," S. Patai, Ed., Interscience, London, 1966, pp 467–470.

(4) C. S. Ng, Ph.D. Thesis, University of Illinois at Chicago Circle, Chicago, Ill., 1973.

(5) R. P. Bell, *Advan. Phys. Org. Chem.*, **4**, 1 (1966).

(6) P. Valenta, *Collect. Czech. Chem. Commun.*, **25**, 853 (1960).

(7) R. P. Bell and J. C. Clunie, *Trans. Faraday Soc.*, **48**, 439 (1952).

(8) E. Lombardi and P. B. Sogo, *J. Chem. Phys.*, **32**, 635 (1960).

(9) L. C. Gruen and P. T. McTigue, *J. Chem. Soc.*, 5217 (1963).

(10) P. Greenzaid, Z. Luz, and D. Samuel, *J. Amer. Chem. Soc.*, **89**, 749 (1967).

(11) P. Federlin, *C. R. Acad. Sci.*, **235**, 44 (1952).

(12) As all reactions were carried out at constant acidity, the acidity dependence of the oxidation reaction is not explicitly considered. Thus all rate constants used in this paper, k_{obsd}, k_H, and k_A, represent acidity-dependent rate constants.

(13) This value is in good agreement with the value of $\rho^* = -1.2$ obtained earlier from a much more limited set of experimental data.[2]

TABLE I

CHROMIUM(VI) OXIDATION OF ALIPHATIC ALDEHYDES IN WATER IN 0.2 M $HClO_4$ AT 25°

Registry no.	Aldehyde	K_d	Second-order rate constant, M^{-1} sec^{-1} × 10^3 k_{obsd}	k_H	k_A
50-00-0	HCHO	0.00055[b]	3.99 ± 0.28	3.99 ± 0.28	7250 ± 522
75-07-0	CH_3CHO	0.67[c,d]	2.80 ± 0.20	4.68 ± 0.31	7.30 ± 0.62
123-38-6	CH_3CH_2CHO	1.4[e]	4.35 ± 0.45	10.5 ± 1.1	7.50 ± 0.79
123-72-8	$CH_3CH_2CH_2CHO$	2.1[e]	4.41 ± 0.20	13.6 ± 0.5	6.47 ± 0.23
630-19-3	$(CH_3)_3CCHO$	4.1[f]	2.04 ± 0.08	10.5 ± 0.5	2.54 ± 0.11
107-20-0	$ClCH_2CHO$	0.027[g]	0.434 ± 0.040	0.445 ± 0.041	16.5 ± 1.5
79-02-7	Cl_2CHCHO[a]		0.0889 ± 0.0087	0.0889 ± 0.0087	
75-87-6	Cl_3CCHO	0.000036[e]	0.00598 ± 0.00069	0.00598 ± 0.00069	166.0 ± 18.0
41162-98-5	$(CH_3)_3CCDO$		0.258		
	$(CH_3)_2CHOH$[h]		0.746 ± 0.071		

[a] The value of the hydration equilibrium constant for Cl_2CHCHO is not available. It is assumed here that this value lies between those for $ClCH_2CHO$ and Cl_3CCHO, thus making $k_{obsd} = k_H$. [b] Reference 6. [c] Reference 7. [d] Reference 8. [e] Reference 9. [f] Reference 10. [g] Reference 11. [h] Included for comparison.

The chromic acid ester of the aldehyde hydrate in the above mechanism is in equilibrium with both the free aldehyde and the hydrate.[14] In principle, it is therefore immaterial whether the ester is thought of as being formed by a carbonyl addition reaction from the free aldehyde or by an esterification reaction from the hydrate. However, the latter proposal is much more useful as it results in an improved ability to understand and predict aldehyde oxidations and their relationship to the closely related oxidations of alcohols. For example, the relatively low reactivity of aromatic aldehydes[16] is readily understood as a consequence of the low degree of hydrate formations in aromatic aldehydes.

It is of interest to compare the ρ^* values determined in this study with the ρ values obtained earlier by Wiberg for a series of aromatic aldehydes in 91% acetic acid.[19,20] As aromatic aldehydes are hydrated only to a very small extent, the observed ρ values have to be compared with ρ^* obtained from the k_A values as defined by eq 2 for aliphatic aldehydes. Considering the difference in the nature of the aldehydes, in the solvent, and in the reactivity constant used, the similarity between Wiberg's values (ρ = 1.02[19] and 0.77[20]) and our value (ρ^* = 0.53) is satisfactory inasmuch as in both cases small positive values were obtained. This similarity offers additional support for our earlier suggestion that aliphatic and aromatic aldehydes react by the same mechanism (Scheme I) in which the rate-limiting step is the oxidative decomposition of a chromic acid ester of an aldehyde hydrate.

Previous investigators have found sizable isotope effects in the oxidation of formaldehyde (k_H/k_D = 6.8)[21] and acetaldehyde.[22] It was of interest to determine the deuterium isotope effect in the chromic acid oxidation of pivaldehyde, because this aldehyde could possibly react with carbon–carbon bond cleavage, leading to a tertiary carbonium ion intermediate. The rather large observed primary isotope effect (k_H/k_D = 7.9) indicates that this aldehyde reacts normally, *i.e.*, with carbon–hydrogen bond breaking in the rate-limiting step.

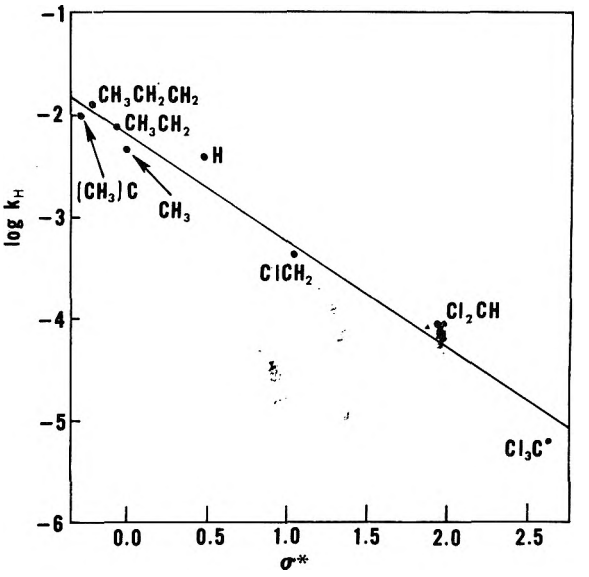


Figure 1.—The chromic acid oxidation of aldehyde hydrates.

Experimental Section

Acetaldehyde (Eastman Chemicals), butyraldehyde (Eastman Chemicals), propionaldehyde (Matheson Coleman and Bell), and chloroacetaldehyde (K & K Laboratory) were purified by fractional distillation through a 14-cm silvered vacuum-jacketed column packed with Nichrome Helipak. Formaldehyde was prepared by heating paraformaldehyde (Eastman Chemicals) in a round-bottom flask by immersing the flask in an oil bath at 180–200°.[23] The formaldehyde gas liberated was introduced into water in an erlenmeyer flask. Dichloracetaldehyde (City Chemicals) and pivaldehyde (K & K Laboratory) were purified by preparative gas–liquid chromatography using a 80 × 0.75 in. silicone rubber SE-30 stainless steel column. Trichloroacetaldehyde (Eastman Chemicals) was distilled through a 14-cm silvered vacuum-jacketed column packed with Nichrome Helipak under nitrogen atmosphere and in the dark.

1-Deuteriopivaldehyde was prepared by the controlled chromic acid oxidation of 1,1-dideuterioneopentyl alcohol,[24] which was prepared by the lithium aluminum deuteride reduction of ethyl pivalate.[25] The ir spectrum of the synthesized 1-deuteriopival-

(14) Evidence for the formation of a chromic acid ester of an aldehyde hydrate has been obtained by Kläning.[15]

(15) U. Kläning, *Acta Chem. Scand.*, **11**, 1313 (1957); **12**, 576 (1958).

(16) Benzaldehyde[17] is about 100 times less reactive than benzyl alcohol,[18] whereas aliphatic aldehydes are generally more reactive than the corresponding primary alcohols.

(17) G. T. Graham and F. H. Westheimer, *J. Amer. Chem. Soc.*, **80**, 3022 (1958).

(18) J. Roček, *Collect. Czech. Chem. Commun.*, **25**, 1052 (1960).

(19) K. B. Wiberg and T. Mill, *J. Amer. Chem. Soc.*, **80**, 3022 (1958).

(20) K. B. Wiberg and W. H. Richardson, *J. Amer. Chem. Soc.*, **84**, 2800 (1962).

(21) T. J. Kemp and W. A. Waters, *Proc. Roy. Soc., Ser. A*, **274**, 480 (1963).

(22) J. W. Cornforth and G. Popjak, *Nature (London)*, **164**, 1053 (1949).

(23) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 397.

(24) C. D. Hurd and R. N. Meinert, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 541.

(25) R. B. Moffett, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 834.

dehyde showed absorptions at 2040 and 2130 cm^{-1} indicative of the C–D stretching of the –CDO group. Its nmr spectrum showed only a single peak at δ 1.1 ppm and no absorption in the δ 8–12-ppm region, indicating the absence of the aldehydic proton. The deuterium content in the aldehyde was determined to be greater than 99% by mass spectroscopy.

All the liquid aldehydes were checked for purity on an F & M 5750 research chromatograph before being dissolved in water for oxidation studies. Because of the high volatility of some of these aldehydes, the concentration of the aqueous solutions was determined analytically. Solutions of formaldehyde, acetaldehyde, propionaldehyde, and butyraldehyde were determined by the hydroxylamine hydrochloride method.[26] Solutions of chloroacetaldehyde and dichloroacetaldehyde were determined by the dinitrophenylhydrazine method.[27]

Kinetic measurements were made by following the decrease in the chromium(VI) concentration spectrophotometrically at 432 nm using a Cary Model 15 double-beam spectrophotometer. All the kinetic experiments were run at 25°. The pseudo-first-order rate constant of the chromium(VI) oxidation of the aldehydes was obtained from the slope of the plot of log $(A_t - A_\infty)$ *vs.* time, where A_t and A_∞ were the absorbance at 432 nm of the reaction mixture at time t and at infinity, respectively. The second-order rate constants, k_{obsd}, were obtained from the pseudo-first-order rate constants and the analytical concentration of the aldehyde.

Registry No.—Chromium, 7440-47-3.

(26) S. Siggia, "Quantitative Organic Analysis via Functional Groups," 2nd ed, Wiley, New York, N. Y., 1963, p 74.

(27) Reference 26, p 92.

Borane Reduction of 3-Substituted 2-Indolinones

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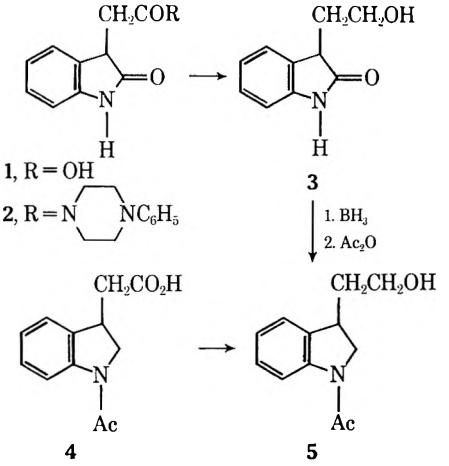
Received April 18, 1973

The utility of borane for the preparation of indolineethanols (9) by reduction of 3-(2-hydroxyethyl)-2-indolinones (3), alkyl 2-oxo-$\Delta^{3,\alpha}$-indolineglycolates (7), and alkyl 2-oxo-3-indolineacetates (8) is illustrated.

We required certain 3-indolineethanols as intermediates for another investigation, and their preparation from 3-substituted 2-indolinones by reductive procedures seemed a distinct possibility. The reduction of 2-indolinones by hydride reagents has been the subject of numerous reports which lack consistency. An early report[1] indicating that lithium aluminum hydride was useful for this purpose is unfounded.[2] However, several investigators have indicated that borane possesses the capacity for such reductions, although the efficiency of this agent for reduction of 2-indolinone and certain 3-substituted derivatives is subject to variability.[2c,3] In this laboratory application of the commercially available reagent[4] to 2-indolinone gave 46% of indoline. Accordingly, the utility of borane for the reduction of certain 3-substituted 2-indolinones was studied.

Initially the preparation of indolineethanol (**9a**) by reduction of the heretofore elusive "oxytryptophol" (**3**)[5] was undertaken. The required 3-(2-hydroxyethyl)-2-indolinone (**3**) was prepared by conversion of 2-oxo-3-indolineacetic acid (**1**)[6] into a mixed carbonic anhydride with ethyl chlorocarbonate; the formation of the anhydride was established by its conversion into the amide **2** with 1-phenylpiperazine (see Scheme I). Reduction of the anhydride with sodium borohydride[7] gave 52% of the required alcohol **3**. This material was then reduced with borane to give 49% of 3-indolineethanol which was characterized as the *N*-acetyl derivative **5**; the last compound also was prepared by reduction of 1-acetylindolineacetic acid (**4**)[8] with borane. The preparation of **5** by the second procedure further illustrates the sharp difference in rate of reaction with borane observed for carboxylic acids and amides.[9]

Scheme I



The above transformations met our requirements in principle. However, the preparation of **5** and congeners from 2-indolinones requires three successive reductions, for the synthesis of **1** can only be accomplished by catalytic hydrogenation of benzyl 2-oxo-$\Delta^{3,\alpha}$-indolineglycolate.[6] Therefore, we sought to circumvent the numerous operations by investigating the reduction of intermediates prior to **1**.

These studies were conducted with derivatives of 2-indolinone (**6a**), 5,6-dimethoxy-2-indolinone (**6b**),[10]

(1) P. A. S. Smith and T. Yu, *J. Amer. Chem. Soc.*, **74**, 1096 (1952).

(2) (a) P. L. Julian and H. C. Printy, *J. Amer. Chem. Soc.*, **71**, 3206 (1949); (b) C. B. Hudson and A. V. Robertson, *Aust. J. Chem.*, **20**, 1699 (1967); (c) K. N. Kilminster and M. Sainsbury, *J. Chem. Soc., Perkin Trans. 1*, 2264 (1972).

(3) (a) H. Plieninger, H. Bauer, W. Bühler, J. Kurze, and U. Lerch, *Justus Liebigs Ann. Chem.*, **680**, 74 (1964); (b) K. M. Biswas and A. H. Jackson, *Tetrahedron*, **24**, 1145 (1968); (c) S. A. Monti and R. R. Schmidt, *ibid.*, **27**, 3331 (1971); (d) H. Sirowej, S. A. Khan, and H. Plieninger, *Synthesis*, 84 (1972).

(4) Ventron, Alpha Inorganics, Beverly, Mass.

(5) E. Wenkert and E. C. Blossey, *J. Org. Chem.*, **27**, 4656 (1962).

(6) P. L. Julian, H. C. Printy, R. Ketcham, and R. Doone, *J. Amer. Chem. Soc.*, **75**, 5305 (1953).

(7) Y. G. Perron, L. B. Crast, J. M. Essery, R. R. Fraser, J. C. Godfrey, C. T. Holdrege, W. F. Minor, M. E. Neubert, R. A. Partyka, and L. C. Cheney, *J. Med. Chem.*, **7**, 483 (1964).

(8) H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, **28**, 2794 (1963).

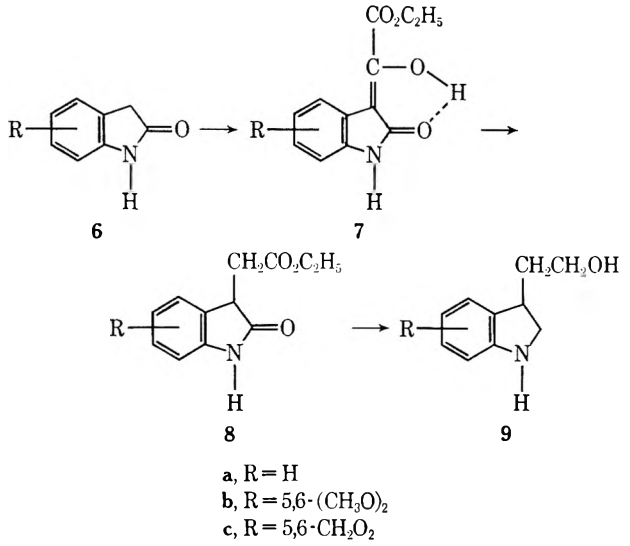
(9) H. C. Brown, P. Heim, and N. M. Yoon, *J. Amer. Chem. Soc.*, **92**, 1637 (1970).

(10) G. N. Walker, *J. Amer. Chem. Soc.*, **77**, 3844 (1955).

and 5,6-methylenedioxy-2-indolinone (**6c**).[11] Our preparation of the last substance from the known[12] 4,5-methylenedioxy-2-nitrophenylacetic acid involved Fischer esterification, catalytic hydrogenation of the ester, and hydrolysis of the reduction product with acetic acid. This three-stage process gave 73% of **6c**, whereas repetition of the literature procedure for its synthesis, involving reduction of the nitrophenylacetic acid in acetic acid, furnished only 26% of product.

Base-catalyzed condensation of the 2-indolinones **6** with ethyl oxalate gave the ethyl 2-oxo-$\Delta^{3,\alpha}$-indolineglycolates **7** (see Scheme II).[13] These isatylidene

SCHEME II



a, R = H
b, R = 5,6-$(CH_3O)_2$
c, R = 5,6-CH_2O_2

derivatives were converted into the ethyl 2-oxo-3-indolineacetates **8** by reduction with zinc amalgam in acetic acid or catalytic hydrogenation.[6] Reduction of substrates **7** and **8** with borane generally proved superior to that of oxytryptophol (**3**) for the preparation of the indolineethanols (see Table I). The reduction of **7a** proved to be the exception, since unidentified side products precluded effective isolation of indolineethanol (**9a**).

Experimental Section

General.—Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Solutions were dried ($MgSO_4$) and concentrated under reduced pressure on a rotary evaporator. The ultraviolet spectra were determined in methanol with a Cary Model 11 recording spectrophotometer, infrared spectra were determined in pressed KBr disks on a Perkin-Elmer Model 21 instrument, and nmr spectra were obtained with a Varian A-60 spectrometer. The petroleum ether used was that fraction having bp 30–60°.

1-(Oxindole-3-acetyl)-4-phenylpiperazine (2).—A solution of 955 mg (5.0 mmol) of oxindole-3-acetic acid (**1**)[6] and 505 mg (5 mmol, 0.7 ml) of triethylamine in 25 ml of tetrahydrofuran was cooled in an ice bath with stirring, and 540 mg (5.0 mmol) of ethyl chloroformate was added dropwise. The resulting mixture was stirred for 10 min, and a solution of 810 mg (5.0 mmol) of 1-phenylpiperazine in 10 ml of tetrahydrofuran was added. The mixture was stirred at 0° for 1 hr and then distributed between ether and water. The organic layer was washed consecutively with 20% acetic acid, water, sodium carbonate solution, and water. The dried solution was evaporated, and the residue was crystallized from acetone–hexane to give 450 mg (27%) of crystals: mp 160–163°; ir max 3.10, 5.84, 6.12, 6.24 μ.

Anal. Calcd for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.48; H, 6.14; N, 12.33.

3-(2-Hydroxyethyl)-2-indolinone (3).—A solution of 2.35 g (12.6 mmol) of oxindole-3-acetic acid (**1**) in 18 ml of tetrahydrofuran at −5° under argon was treated with 1.71 ml of triethylamine and then 1.53 ml of ethyl chlorocarbonate. The mixture was stirred at −5° for 30 min and then filtered. The filtrate was added dropwise to a cold solution of 1.16 g of sodium borohydride in 18 ml of water, and the solution was then stirred at ambient temperature for 2 hr. The reaction mixture was rendered strongly acid with hydrochloric acid and extracted with ethyl acetate. The organic extracts were washed successively with saline, sodium hydroxide solution, and saline. The dried organic solution was evaporated to give a gum which crystallized from ether to furnish 1.11 g (52%) of white crystals, mp 107–110°. The analytical sample was obtained from acetone–petroleum ether and had mp 111–112°; ir max 3.00, 3.15, 5.92, 6.16 μ.

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.62; H, 6.35; N, 7.88.

4,5-Methylenedioxy-2-nitrophenylacetic Acid.—A suspension of 25 g of 4,5-methylenedioxyphenylacetic acid[14] in 110 ml of acetic acid was stirred at 15° while 40.5 ml of concentrated nitric acid was added in portions maintaining the temperature at 40°. The mixture was stirred for an additional 40 min and then added to 800 ml of ice water. The product was collected as 24.5 g of yellow crystals, mp 185–188°. A sample recrystallized from methanol had mp 186–188°; ir max 6.57, 7.56 μ; $\delta_{TMS}^{CDCl_3}$ 3.92 (s, 2, CH_2CO_2H), 6.14 (s, 2, OCH_2O), 6.82 (s, 1, 6-H), 7.61 (s, 1, 3-H).

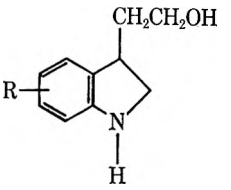
Anal. Calcd for $C_9H_7NO_6$: C, 48.01; H, 3.13; N, 6.22. Found: C, 48.13; H, 3.19; N, 6.24.

Fischer esterification of this material (25 g) with methanol–sulfuric acid gave 23.6 g (88%) of the methyl ester, mp 106–108°.

5,7-Dihydro-6*H*-1,3-dioxolo[4,5-*f*]indol-6-one (6c).—A mixture of 27.7 g (0.1 mol) of methyl 2-nitro-4,5-methylenedioxyphenylacetate and 1.4 g of 10% Pd/C catalyst in 200 ml of ethanol was shaken with hydrogen until the theoretical amount of hydrogen was absorbed. The reaction mixture was filtered and evaporated under reduced pressure to give methyl 2-amino-4,5-methylene-

TABLE I

YIELD OF INDOLINEETHANOLS *via* BORANE REDUCTION OF 2-INDOLINONES



2-Indolinone substrate	Indolineethanol product R	Yield, %
3-(2-Hydroxyethyl)-2-indolinone (**3**)	H[a]	49
Ethyl 2-oxo-3-indolineacetate (**8a**)	H[a]	55
1-Acetyl-3-indolineacetic acid (**4**)	H[a]	73
Ethyl 5,6-dimethoxy-2-oxo-3-indolineacetate (**8b**)	5,6-$(CH_3O)_2$[a]	79
Ethyl 5,6-dimethoxy-2-oxo-$\Delta^{3,\alpha}$-indolineglycolate (**7b**)	5,6-$(CH_3O)_2$[a]	47
Ethyl 5,6-dihydro-6-oxo-7*H*-1,3-dioxolo[4,5-*f*]indole-7-acetate (**8c**)	5,6-OCH_2O[b]	57
Ethyl 5,6-dihydro-6-oxo-7*H*-1,3-dioxolo[4,5-*f*]indole-$\Delta^{7,\alpha}$-glycolate (**7c**)	5,6-OCH_2O[b]	43

[a] Characterized as the 1-acetyl derivative. [b] Characterized as the acetate ester of the 1-acetyl derivative.

(11) This name is used to maintain consistency; Chemical Abstracts nomenclature is 5,7-dihydro-6*H*-1,3-dioxolo[4,5-*f*]indol-6-one.

(12) T. Kametani, O. Umezawa, S. Shibuya, K. Ogasawara, M. Ishiguro, and D. Mizuno, *Yakugaku Zasshi*, **83**, 851 (1963); *Chem. Abstr.*, **60**, 449b (1964).

(13) L. Horner, *Justus Liebigs Ann. Chem.*, **548**, 117 (1941).

(14) (a) K. Kindler and T. Gehlhaar, *Arch. Pharm.* (*Weinheim*), **274**, 377 (1936); (b) T. R. Shepard, H. D. Porter, J. F. Noth, and C. K. Simmans, *J. Org. Chem.*, **17**, 568 (1952).

dioxyphenylacetate as a white solid. The product from three such reductions was dissolved in 360 ml of acetic acid, purged with argon, and heated at reflux temperature for 1 hr. The hot solution was diluted with water while stirring until crystals appeared. The mixture was cooled to give 44.0 g (83%) of product as crystals, mp 223–226° dec (lit.[12] mp 216–217° dec).

Preparation of 2-Oxo-$\Delta^{3,\alpha}$-indolineglycolates (7).—The following preparation of ethyl 5,6-dimethoxy-2-oxo-$\Delta^{3,\alpha}$-indolineglycolate (**7b**) illustrates the general procedure.

To a solution of 4.82 g (25 mmol) of 5,6-dimethoxyoxindole in 50 ml of dimethylformamide stirred in an ice bath under an argon atmosphere was added 1.25 g of a sodium hydride in oil dispersion (60.2% concentration). The mixture was stirred for 30 min and then a solution of 5.35 g (36.7 mmol) of diethyl oxalate in 25 ml of dimethylformamide was added dropwise. The solution was stirred at ambient temperature for 18 hr and then diluted with 150 ml of water. The aqueous solution was stirred in an ice bath and acidified with hydrochloric acid. The resultant red solid was recrystallized from acetone to give 4.55 g (66%) of red crystals: mp 183–185° dec; ir max 5.75, 6.00, 6.14, 6.57, 6.73 μ; $\delta_{TMS}^{DMSO\text{-}d_6}$ 1.33 (t, 3, J = 8.5 Hz, CH_3CH_2), 3.75, 3.80 (s, 3 each, OCH_3), 4.40 (q, 2, J = 8.5 Hz, CH_3CH_2), 6.64 (s, 1, 7-H), 7.59 (s, 1, 4-H).

Anal. Calcd for $C_{14}H_{15}NO_6$; C, 57.33; H, 5.16; N, 4.78. Found: C, 56.83; H, 5.14; N, 4.26.

Ethyl 5,6-dihydro-6-oxo-7*H*-1,3-dioxolo[4,5-*f*]indole-$\Delta^{7,\alpha}$-glycolate (7c) was similarly obtained in 93% yield. Recrystallized from acetone it had mp 246–248° dec; ir max 5.75, 5.97 μ; $\delta_{TMS}^{DMSO\text{-}d_6}$ 1.33 (t, 3, J = 7.5 Hz, CH_3CH_2), 4.37 (q, 2, J = 7.5 Hz, CH_3CH_2), 6.00 (s, 2, OCH_2O), 6.65 (s, 7-H), 7.43 (s, 4-H).

Anal. Calcd for $C_{13}H_{11}NO_6$: C, 56.32; H, 4.00; N, 5.05. Found: C, 56.50; H, 3.94; N, 4.97.

Preparation of Ethyl 2-Oxo-3-indolineacetates (8).—The following preparation of the 5,6-dimethoxy derivative **8b** is illustrative. To a suspension of 0.73 g of ethyl 5,6-dimethoxy-2-oxo-$\Delta^{3,\alpha}$-indolineglycolate (**7b**) in 50 ml of acetic acid was added freshly prepared zinc amalgam (from 11 g of zinc and 1.1 g of mercuric chloride). The mixture was stirred under reflux for 16 hr. The mixture was cooled and filtered, and the filtrate was reduced in volume to 10 ml. The residue was diluted with 50 ml of water and extracted with ether. The ether extract was washed with saturated sodium carbonate solution and saturated sodium chloride solution, and evaporated. The resultant solid mass crystallized from acetone–petroleum ether to give 320 mg (46%) of the product: mp 123–124°; ir max 3.14, 5.77, 6.12 μ; $\delta_{TMS}^{CDCl_3}$ 1.23 (t, 3, J = 7.0 Hz, CH_3CH_2), 2.80, 3.04 (m, 2, J_{gem} = 17.0 Hz, $J_{A,B}$ = 8.0 Hz, $J_{A',B}$ = 5.0 Hz, CH_2), 3.78 (m, 3-H), 4.17 (q, 2, J = 7.0 Hz, CH_3CH_2), 6.57, 6.90 (each s, aryl H).

Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.34; H, 6.21; N, 5.16.

Ethyl 5,6-dihydro-6-oxo-7*H*-1,3-dioxolo[4,5-*f*]indole-7-acetate (8c) was prepared similarly in 73% yield: ir max 3.12, 5.75, 5.82, 5.98, 6.10 μ; $\delta_{TMS}^{DMSO\text{-}d_6}$ 1.11 (t, 3, J = 7.5 Hz, CH_3CH_2), 2.75–2.92 (m, 2, CH_2CO_2), 3.59 (d t, 1, $CHCH_2CO_2$), 4.04 (q, 2, J = 7.5 Hz, CH_3CH_2), 5.92 (s, 2, OCH_2O), 6.50 (s, 1, 4-H), 6.89 (s, 1, 8-H).

Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.41; H, 4.92; N, 5.31.

Borane Reductions. General Procedure.—A solution of 1.95 g (7.0 mmol) of ethyl 5,6-dimethoxy-2-oxo-3-indolineacetate (**8b**) in 100 ml of tetrahydrofuran stirred in an ice bath under an argon atmosphere was treated with 40 ml of 1 *M* borane in tetrahydrofuran. The mixture was stirred for 15 hr at ambient temperature and then heated under reflux for 18 hr. The solvent was removed, and the residue was heated at 100° with 100 ml of 1 *N* hydrochloric acid. The acid solution was cooled, washed with ethyl acetate, chilled in an ice bath, and made alkaline with aqueous sodium hydroxide solution. The alkaline solution was extracted with ethyl acetate. The organic extract was washed with saline, dried, and evaporated to give 1.23 g (79%) of 5,6-dimethoxy-3-indolineethanol (**9b**) as a gum. Schotten–Bauman acetylation gave **1-acetyl-5,6-dimethoxy-3-indolineethanol**, mp 148–150°, after recrystallization from acetone–petroleum ether: uv max 216, 261, 303 mμ (ϵ 19,100, 15,400, 8200); ir max 2.95, 6.10, 6.22 μ.

Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.52; H, 7.30; N, 5.15.

The reduction of other oxindole derivatives is summarized in Table I, and the characterization of the products is given below.

1-Acetyl-3-indolineethanol (**5**) was obtained from ether as white crystals, mp 49–52°.

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.97; H, 7.43; N, 6.56.

5-Acetyl-6,7-dihydro-5*H*-1,3-dioxo[4,5-*f*]indole-7-ethyl acetate was prepared by acetylation of the reduction product in pyridine and obtained from acetone–petroleum ether as white crystals: mp 93–94°; ir max 5.75, 6.01 μ.

Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.73; H, 5.91; N, 4.97.

Acknowledgment.—We are indebted to Messrs. W. Fulmor and L. Brancone and their associates for supplying spectral data and microanalyses, respectively.

Registry No.—**1**, 2971-31-5; **2**, 40940-09-8; **3**, 3690-95-7; **4**, 40118-10-3; **5**, 40118-11-4; **6c**, 25326-30-1; **7b**, 40119-20-8; **7c**, 40118-21-6; **8a**, 40940-16-7; **8b**, 40118-13-6; **8c**, 40118-22-7; 1-phenylpiperazine, 92-54-6; 4,5-methylenedioxy-2-nitrophenylacetic acid, 40118-17-0; 4,5-methylenedioxy-2-nitrophenylacetic acid methyl ester, 40118-18-1; 4,5-methylenedioxyphenylacetic acid, 2861-28-1; 5,6-dimethoxyoxindole, 6286-64-2; diethyl oxalate, 95-92-1; borane, 13283-31-3; 1-acetyl-5,6-dimethoxy-3-indolineethanol, 40118-15-8; 5-acetyl-6,7-dihydro-5*H*-1,3-dioxolo[4,5-*f*]indole-7-ethyl acetate, 40118-24-9.

Stereochemistry of Methyldichlorosilane Additions to Pentadienes[1]

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Received December 29, 1971

The reaction of methyldichlorosilane with *cis*-1,3-, *trans*-1,3-, and 1,4-pentadienes in the presence of chloroplatinic acid has been investigated. All products were converted into the trimethylsilyl derivatives for glpc analysis and identification purposes. In the reaction involving 1,4-pentadiene, three products were found in a 75.5% yield with the following composition after methylation: 1-trimethylsilyl-4-pentene (87.2%); *cis*-1-trimethylsilyl-2-pentene (9.3%); and *cis*-1-trimethylsilyl-3-pentene (3.5%). The reaction with *trans*-1,3-pentadiene gave three products in a 74.6% yield with the following composition after methylation: *cis*-1-trimethylsilyl-2-pentene (42.0%); *trans*-2-trimethylsilyl-3-pentene (39.1%); and *trans*-1-trimethylsilyl-2-pentene (18.9%). The reaction of *cis*-1,3-pentadiene gave five products in a 82.2% yield, with the following composition after methylation: 1-trimethylsilyl-4-pentene (1.3%); *cis*-1-trimethylsilyl-2-pentene (23.2%); *cis*-1-trimethylsilyl-3-pentene (60.8%); *trans*-2-trimethylsilyl-3-pentene (10.5%); and *trans*-1-trimethylsilyl-2-pentene (4.2%). A mechanism accounting for the products is proposed. This involves a platinum–diene–silane complex which then gives the various products. Besides 1,2 addition, in which silicon is found in the 1 position, reverse 1,2 addition, in which silicon is bonded to the 2 position, and 1,4 addition with silicon in the 1 position occur. This reverse 1,2 addition is accounted for by the stabilizing effect of the second double bond, and the predominance of cis products resulting from 1,4 addition is thought to be due to the original diene reacting in the cisoid conformation.

Though platinum and chloroplatinic acid catalyzed[1-8] additions and thermally induced[9] additions of silanes to dienes have been reported previously, the influence of systematic changes in the structure of the diene on the stereochemistry of the reaction has not been determined. The addition of methyldichlorosilane to *cis*-1,3-, *trans*-1,3-, and 1,4-pentadiene using chloroplatinic acid as a catalyst was therefore undertaken.

The addition of silanes to simple olefins and acetylenes, using a chloroplatinic acid catalyst, has revealed some unique properties of this catalyst system. Silicon hydrides add to 1-alkenes in such a way that the silicon becomes attached to the terminal position, and the hydrogen adds to the internal portion of the double bond.[10] If the double bond is internal, as in 2-pentene, it has been shown that migration often occurs, with silicon again being bonded to the terminal carbon atom.[10] In the case of acetylenes, silanes add in a cis manner and no bond migration takes place.[11] Optically active silanes have been added to double and triple bonds,[12] and, in the cases studied to date, the silane retains its optical activity.

The additions of methyldichlorosilane to the pentadienes were carried out in cyclohexane solvent using catalytic amounts of an isopropyl alcohol solution of chloroplatinic acid. Methyldichlorosilylpentenes were generally obtained in high yields and then methylated for glpc analysis.

$$n\text{-}C_5H_8 + CH_3SiCl_2H \xrightarrow{H_2PtCl_6} CH_3Cl_2SiC_5H_9 \xrightarrow[\text{or } CH_3MgBr]{CH_3MgCl} (CH_3)_3SiC_5H_9$$

Since the reactions may involve migration as well as 1,2 and 1,4 additions to the diene system, as many as 16 isomers are possible. The reaction was found to be much more stereoselective than this (see Table I), and there were never more than five product isomers.

For the nonconjugated 1,4-pentadiene, simple addition to one of the double bonds, followed by methylation, leads to the principal reaction product 1-trimethylsilyl-4-pentene (1). This was shown to be identical with 1-trimethylsilyl-4-pentene prepared by an independent method.[13] The mode of addition is comparable to that reported by Vdovin and Petrov[4] for chloroplatinic acid catalyzed addition of methyldichlorosilane to 1,5-hexadiene, and the platinum-catalyzed addition of trichloro- and triethylsilane to 1,5-cyclooctadiene.[3]

Previous reports on the addition of silanes to conjugated dienes have involved 1,4 addition. Bailey and Pines[2] prepared 1-trichlorosilyl-2-butene by the platinum-catalyzed reaction of trichlorosilane with butadiene, and Mironov and Nepomnina[8] obtained 43% of 2-methyldichlorosilyl-3-pentene by 1,4 addition to 1,3-pentadiene using chloroplatinic acid catalyst. Similarly, the additions of silanes to isoprene[6] have been found to occur by the 1,4 mode of addition.

$$CH_2{=}CH{-}\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH_2 + HSi{\equiv} \xrightarrow{H_2PtCl_6} CH_3CH{=}\overset{\displaystyle CH_3}{\overset{|}{C}}CH_2Si{\equiv}$$

Using *cis*- and *trans*-1,3-pentadiene, we have found that both simple and conjugate addition occurs with methyldichlorosilane and chloroplatinic acid.

trans-1,3-Pentadiene gives three monoadducts upon reaction with methyldichlorosilane catalyzed by chloroplatinic acid, as shown by the isolation and characterization of the methylated products.

Structure 2 would be obtained from 1,4 addition to the s-cis form of *trans*-1,3-pentadiene. The struc-

(1) Taken from the Ph.D. Thesis of C. Zullig, University of Detroit, 1969.

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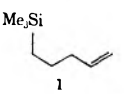
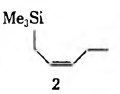
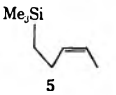
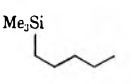
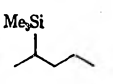
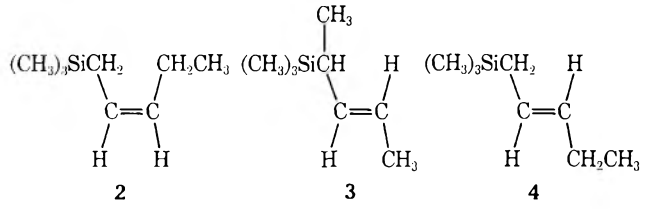
TABLE I

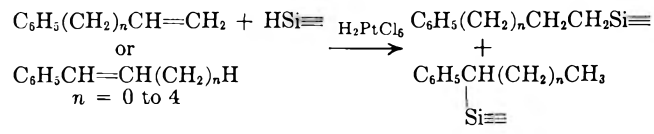
TRIMETHYLSILYLPENTENES PRODUCED FROM THE PENTADIENES AND THEIR HYDROGENATION PRODUCTS[a]

Registry no.	Pentadiene	Addition, %	Methylated product composition, %					Hydrogenation products, %	
			 1	 2	 3	 4	 5		
591-93-5	1,4-	75.5	87.2	9.3			3.5	97.7	2.3
2004-70-8	*trans*-1,3-	74.6		42.0	39.1	18.9		62.6	37.4
1574-41-0	*cis*-1,3-	82.2	1.3	23.2	10.5	4.2	60.8	91.1	8.9

[a] Results cited are area per cent from glpc analysis on a 26-ft UCON Polar column.



ture was confirmed by independent synthesis. Product **4** would also result from 1,4 addition, and was identified by comparison with an independently synthesized sample. The simple 1,2 addition probably accounts for the *trans*-2-trimethylsilyl-3-pentene (**3**), since the original geometry of the double bond in *trans*-1,3-pentadiene is preserved. The appearance of the silyl group at the second carbon is somewhat surprising in view of the work by Speier, Webster, and Barnes[10] which shows a strong preference of the silyl group for the terminal position. However, Musolf and Speier[14] have shown that silane additions to phenyl-



alkenes produce two products, one with silicon at the terminal position of the alkyl group, and the other with the silicon α to the aromatic ring. The preference of the silicon atom for a carbon α to a center of unsaturation would seem to be the most important factor in the formation of **3**.

The addition to *cis*-1,3- pentadiene was somewhat more complex, as five different products resulted, and, when an excess of diene was employed, 11.8% isomerization of the unreacted diene to the *trans*-1,3-pentadiene was detected (see Table II). This isomeriza-

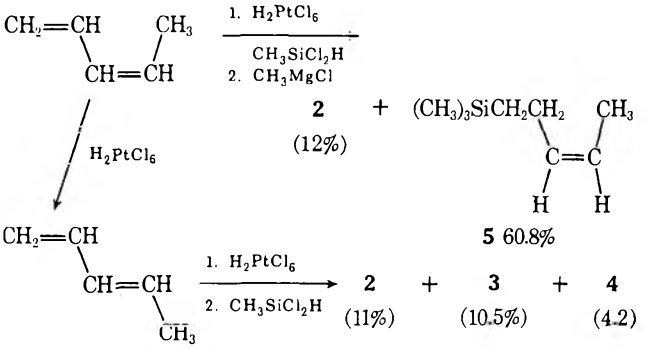
TABLE II

ISOMERIZATION OF PENTADIENES CONCURRENT WITH ADDITION[a]

Starting diene	Addition product yield, %	Isomerized pentadiene % composition 1,4-	*cis*-1,3-	*trans*-1,3-
1,4-	22.9	93.8	1.9	4.3
cis-1,3-	19		88.2	11.8
trans-1,3-	72.5		1.1	98.9

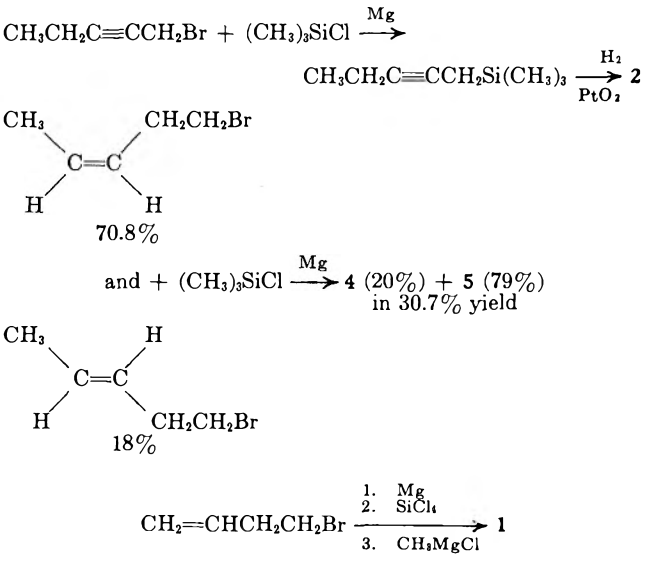
[a] Excess pentadiene analyzed by glpc after 24 hr at 58° with chloroplatinic acid, methyldichlorosilane, and cyclohexane. See Experimental Section for details.

tion was negligible in the cases of the other two dienes. If it is assumed that some of the products (Table I) from the *cis*-1,3-pentadiene arise from the *trans*-1,3-pentadiene produced by isomerization, an approximate product composition due solely to the cis isomer can be determined. *trans*-2-Trimethylsilyl-3-pentene (**3**) should only be produced by 1,2 addition to the *trans*-1,3-pentadiene. On this basis 11% of compound **2** and all of compound **4** can be accounted for by the isomerization of the starting diene. The origin of **1** is not known, but it amounts to only 1.3% of the product. The major product, *cis*-1-trimethyl-



silyl-3-pentene (**5**), is due to simple 1,2 addition to the terminal double bond, while **2** would be due to 1,4 addition to the s-cis form of the diene.

All of the trimethylsilylpentenes formed by addition to the pentadienes were prepared by independent methods with the exception of **3**. Hydrogenation



of the trimethylsilylpentenes produced by addition to *trans*-1,3-pentadiene yielded only 1- and 2-pentyl-

(14) M. C. Musolf and J. L. Speier, *J. Org. Chem.*, **29**, 2519 (1964).

trimethylsilanes (62.6 and 37.4%, respectively). The 2-pentyltrimethylsilane was shown to be derived from **3**, since separate hydrogenation of **2**, the only other possible source, yielded only 1-pentyltrimethylsilane. Product **3** was further characterized by nmr and ir spectra where a band at 1005 cm^{-1}, characteristic of trans olefins, was evident. All attempts to synthesize **3** independently were unsuccessful. The other adducts (**1**, **2**, **4**, and **5**), in addition to having glpc retention times identical with those of the authenic samples, produced nmr, ir, and hydrogenation data consistent with the structures given.

In order to exclude, if possible, any prior isomerization of the diene, an excess of each pentadiene was used for the additions of methyldichlorosilane. The unreacted pentadiene after 24 hr under reaction conditions was analyzed by glpc. The results are summarized in Table II. Only the *cis*-1,3-pentadiene shows significant isomerization and some part of the addition products may arise from the *trans*-1,3-pentadiene produced in the isomerization. Isomerization of the adducts was not significant, since varying the time between completion of the reaction and the work-up of the reaction mixture did not change the product composition. In addition, each diene produced a distinctive product composition, so that isomerization toward any kind of equilibrium composition can be ruled out.

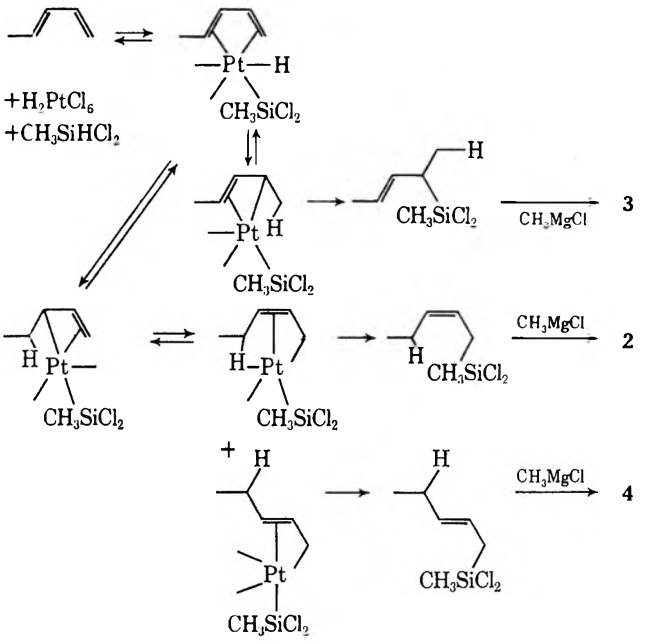
There is little selectivity in the reaction of the methyldichlorosilylpentenes with methylmagnesium chloride, so that analysis of the trimethylsilypentenes, which are more convenient to handle, gave good results. For example, a mixture of three methyldichlorosilylpentenes (in the ratio 1.08:1:0.74) produced in a competition reaction between *cis*- and *trans*-1,3-pentadiene gave the corresponding trimethylsilylpentenes in the ratio 1.11:1:0.67. This competition reaction, in which 0.1 mol of *cis*-1,3-pentadiene and 0.1 mol of *trans*-1,3-pentadiene were allowed to compete for 0.1 mol of methyldichlorosilane, demonstrated the more rapid reaction of the *trans*-1,3-pentadiene since only 27.6% of the unreacted *trans*-1,3-pentadiene remained while 72.4% of *cis*-1,3-pentadiene was left.

Chalk and Harrod[15] have formulated a mechanism for platinum-catalyzed additions of silanes to olefins which accounts for the isomerization and terminal silane addition often observed with nonterminal olefins.[10,16-18] A similar mechanism can account for the results of methyldichlorosilane addition to pentadienes using chloroplatinic acid, although both double bonds of the conjugated pentadienes must sometimes be involved in the platinum complex to account for the stereoselectivity of the addition and the major amounts of 1,4 addition found. The involvement of dienes, as bidentate ligands, in platinum-catalyzed silane additions has been proposed by Kuivila and Warner[7] for the rigid bicycloheptadiene system and probably occurs in other chloroplatinic acid catalyzed additions to dienes.[19] In fact, stable Pt(II)–diene complexes have been prepared,[20-22] although no attempt was made to add silanes.

The addition products of methyldichlorosilane which involve only the terminal double bond, **1** for 1,4-pentadiene, **3** for *trans*-1,3-pentadiene, and **5** for *cis*-1,3-pentadiene, can be accounted for by a simple platinum–olefin complex. The large amount of simple 1,2 addition and the small amount of conjugate or 1,4 addition for the *cis*-1,3-pentadiene as compared to *trans*-1,3-pentadiene must result from differences in the s-cis form of the diene, which is apparently preferred for the platinum–diene complex. The terminal methyl group must either interfere with the

coplanarity of the s-cis form of diene, which may be a requirement for stable complex formation, or prevent the close approach of the platinum. Chatt[20,21] has shown that, in general, Pt(II)–diene complexes are more stable than Pt(II)–olefin complexes but that there are differences among dienes that must be ascribed to the geometry of the system. The competition between *cis*-1,3-pentadiene and *trans*-1,3-pentadiene for methyldichlorosilane further illustrates the difficulty in forming a diene complex with *cis*-pentadiene, since 72% of the *trans*-1,3-pentadiene was transformed into products but only 28% of the *cis*-1,3-pentadiene reacted with the methyldichlorosilane.

A basic mechanism that can account for the 1,2- and 1,4-addition products of *trans*-1,3-pentadiene can be written in the following way.



The importance of the s-cis or cisoid form can be seen for the *trans*-1,3-pentadiene, and the reluctance of the *cis*-1,3-pentadiene to assume this form during reaction has also been demonstrated. The 1,4-pentadiene yields some isomerized product which may arise from addition to a cyclic complex or just as likely from isomerization of the diene prior to addition.

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(16) J. C. Saam and J. L. Speier, *J. Amer. Chem. Soc.*, **80**, 4104 (1958).
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(18) R. A. Benkeser, S. Dunny, G. S. Li, P. G. Nerlekar, and S. D. Work, *J. Amer. Chem. Soc.*, **90**, 1871 (1968).
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(21) J. Chatt, *J. Chem. Soc.*, 2496 (1957).
(22) E. W. Abel, M. A. Bennet, and G. Wilkenson, *J. Chem. Soc.*, 3178 (1959).

Experimental Section

All the pentadienes were obtained from Chemical Samples Co. and were shown to be better than 99% pure by glpc analysis. Routine glpc work was done on a Varian Aerograph Model A-90P gas chromatograph using a 26 ft × 0.25 in. 15% UCON Polar on 60–80 mesh firebrick column (column A) and 28 ft × 0.50 in. preparative column of 15% UCON Polar on 30–60 mesh firebrick (column B). Separation and identification of isomers were further checked using a 0.125 in. diameter, 300 ft Perkin-Elmer 1050 capillary column coated with Apiezon (column C) on a Perkin-Elmer 800 gas chromatograph. Infrared spectra were obtained using a Beckman IR-5, a Beckman IR-12, and a Perkin-Elmer Model 337. The nmr spectra were taken on a Varian A-60A.

Addition of Methyldichlorosilane to 1,4-Pentadiene.—A mixture of 25 ml of cyclohexane and 50 μl of 0.2 *M* chloroplatinic acid (in isopropyl alcohol) was stirred while an equal molar mixture of 20 ml (13.6 g, 0.20 mol) of 1,4-pentadiene and 21.0 ml (23.0 g, 0.20 mol) of methyldichlorosilane was added dropwise. Approximately 15 min after the addition was completed, an exothermic reaction took place and the temperature rose to 93°. After the initial reaction had subsided, the contents of the flask were heated for 24 hr at 93°. Distillation under reduced pressure afforded 27.48 g (75.5% yield) of methyldichlorosilylpentenes, bp 60–63° (15 mm), n^{24}D 1.4191.

The methyldichlorosilylpentenes from the reaction above were added dropwise to 125 ml of 3 *M* methylmagnesium chloride. After the addition, the mixture was refluxed for 3 hr and cooled. The contents of the flask were poured into ice water, and ammonium chloride and hydrochloric acid were added until the ether and aqueous layers became clearly separable. The organic layer was separated from the aqueous layer, and this aqueous layer was extracted three times with ether. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was distilled under reduced pressure, yielding 14.10 g (66.2% yield) of trimethylsilylpentenes, bp 56° (43 mm). Analysis by glpc using column A gave the following product composition: **1**, 1-trimethylsilyl-4-pentene (87.2%); **2**, *cis*-1-trimethylsilyl-2-pentene (9.3%); and **5**, *cis*-1-trimethylsilyl-3-pentene (3.5%). Product **1** was separated on column B using preparative gas chromatography. The infrared spectrum of 1,1-trimethylsilyl-4-pentene showed peaks at 3095 (vinyl CH), 2950, 2870, (CH), 1645 (CC), 1460 (CH), 1440 (vinyl CH), 1420 ($SiCH_3$), 1255 ($SiCH_3$), 915 (vinyl CH), 850 (SiC), and 695 cm^{-1} (SiC).

Anal. Calcd for $C_8H_{18}Si$: C, 67.50; H, 12.77. Found: C, 67.50; H, 12.72.

Hydrogenation of the Trimethylsilylpentene Mixture.—A 12% solution by volume of trimethylsilylpentenes from the reaction above in 50 ml of ethyl acetate was hydrogenated over platinum oxide (0.1 g) at 40 psi initial pressure. The products and reactants were analyzed by glpc using column A. Two products were formed in a 97% yield. The first product was 2.3% of the mixture and had the same retention time as 2-pentyltrimethylsilane. The second (97.7%) corresponded to 1-pentyltrimethylsilane.

Addition of Methyldichlorosilane to *trans*-1,3-Pentadiene.—The reaction was identical with that described for 1,4-pentadiene, except that this reaction was not exothermic and had to be continually heated for 24 hr to achieve a solution temperature of 95°. Distillation yielded 27.27 g (74.6% yield) of methyldichlorosilylpentenes, bp 64–65° (23 mm).

The apparatus and general procedure for methylating the methyldichlorosilylpentenes were the same as described above. Methylmagnesium chloride (0.660 mol in 220 ml of ether solution) was used to react with 27.27 g (0.149 mol) of methyldichlorosilylpentenes. After hydrolysis, extraction, and drying over anhydrous sodium sulfate, the products were distilled, affording 11.22 g (53.1% yield) of trimethylsilylpentenes, bp 46–47° (43 mm).

The product mixture was injected into a gas chromatograph using column A as previously described. The presence of three products was shown: **3**, *trans*-2-trimethylsilyl-3-pentene (39.1%); **4**, *trans*-1-trimethylsilyl-2-pentene (18.9%); and **2**, *cis*-1-trimethylsilyl-2-pentene (42.0%). In addition, this product was injected into the capillary column C to give **2** (36.9%), **5** (5.1%), **3** (39.1%), and **4** (18.2%). Using preparative gas chromatography, products **2**, **3**, and **4** were separated on column B at 73°.

The following spectra of **3**, *trans*-2-trimethylsilyl-3-pentene, was obtained: ir (neat) 3050 (vinyl CH), 2990 (CH), 2900 (CH), 1675 (CH), 1470 (CH), 1395 ($SiCH_3$), 1265 ($SiCH_3$), 1005 (trans olefin), 860 (SiC), and 705 cm^{-1} (SiC); nmr τ 10.37 (s, 9), 9.28 (d, 3), 8.92 (m, 1), 8.68 (d, 3), 5.02 (m, 2).

Anal. Calcd for $C_8H_{18}Si$: C, 67.50; H, 12.77. Found: C, 67.58; H, 12.60.

Isolated **4**, *trans*-1-trimethylsilyl-2-pentene, n^{25}D 1.465, had the following infrared spectrum: 2900 (CH) 1650 (C=C), 1460 (CH), 1650 (C=C), 1460 (CH), 1400 ($SiCH_3$), 1250 ($SiCH_3$), 990 (trans olefin), and 850 cm^{-1} (SiC).

Anal. Calcd for $C_8H_{18}Si$: C, 67.50; H, 12.77. Found: C, 67.73; H, 12.85.

cis-1-Trimethylsilyl-2-pentene (**2**), n^{25}D 1.4259, had the following spectra: ir (neat) 3020 (CH), 2990 (CH), 2905 (CH), 1665 (C=C), 1470 (CH), 1425 (cis olefin), 1440 ($SiCH_3$), 1255 ($SiCH_3$), 860 (SiC), 705 (SiC), and 670 cm^{-1} (cis olefin); nmr τ 10.30 (s, 9), 9.35 (t, 3), 8.83 (d, 2), 8.27 (m, 2), and 5.00 (m, 2).

Anal. Calcd for $C_8H_{18}Si$: C, 67.50; H, 12.77. Found: C, 67.25; H, 12.52.

Hydrogenation of Trimethylsilylpentene Mixture.—The procedure was the same as that described for the hydrogenation of trimethylsilylpentenes from the 1,4-pentadiene addition, except that for complete hydrogenation to take place, 16 hr under a pressure of 40 psi was necessary. The reaction was followed by glpc using column A. The overall yield of products was 88% and the product composition was 37.4% 2-pentyltrimethylsilane and 62.6% 1-pentyltrimethylsilane.

Hydrogenation of *cis*-1-Trimethylsilyl-2-pentene.—A 12% solution of **2**, *cis*-1-trimethylsilyl-2-pentene, in 25 ml of ethyl acetate was hydrogenated separatedly over platinum oxide. The procedure was identical with that described above. Product **2** yielded 1-pentyltrimethylsilane exclusively. The yield was 99% as determined by glpc.

Addition of Methyldichlorosilane to *cis*-1,3-Pentadiene.—The reaction was identical with that of *trans*-1,3-pentadiene. Distillation gave 29.55 g (82.2% yield) of methyldichlorosilylpentenes, bp 75–76° (43 mm).

The methylation procedure was identical with that already described for the methyldichlorosilanes from *trans*-1,3-pentadiene, except that 29.55 g (0.161 mol) of methyldichlorosilylpentenes was used. The yield was 22.88 g (75.5%) of trimethylsilylpentenes, bp 52–56° (43 mm). Gas chromatography using column A showed the presence of five products: **3** (10.5%), **4** (4.2%), **1** (1.3%), **2** (23.2%), and **5** (60.8%). Using column C five peaks were also found: **3** (16.0%), **4** (4.1%), **1** (2.0%), **2** (1.3%), and **5** (76.6%). Preparative gas chromatography, using column B, was used to obtain **5**: ir (neat) 3070 (CH), 3010 (CH), 2950 (CH), 1660 (C=C), 1450 (CH), 1405 ($SiCH_3$), 1250 ($SiCH_3$) 850 (SiC), 695 (SiC), and 675 cm^{-1} (cis olefin); nmr (impure sample) τ 10.20 (s), 9.60 (m), 8.63 (d), 4.82 (m).

Anal. Calcd for $C_8H_{18}Si$: C, 67.50; H, 12.77. Found: C, 67.35; H, 12.60.

Hydrogenation of Trimethylsilylpentene Mixture.—This hydrogenation procedure was identical with the hydrogenation of the previous trimethylsilylpentene mixtures. By glpc using column A it was shown that hydrogenation proceeded to give a 97% yield of two products, 2-pentyltrimethylsilane (8.9%) and 1-pentyltrimethylsilane (91.1%).

Preparation of 1-Pentyltrimethylslane.—The procedure of Whitmore, *et al.*,[23] was followed by allowing 15.1 g (0.10 mol) of 1-bromopentane to react with 2.5 g (0.10 mol) of magnesium turnings in 100 ml of dry ether, and then adding 21.8 g (0.20 mol) of trimethylchlorosilane in 20 ml of dry ether. The dried ether layer was distilled to give 5.2 g (36%) of 1-pentyltrimethylsilane: bp 137–138°; n^{20}D 1.4096 (lit.[23] bp 139.3°; n^{25}D 1.4069); ir (neat) 2800 (CH), 1460 (CH), 1410 ($SiCH_3$), 1250 ($SiCH_3$), 850 (SiC), and 695 cm^{-1} (SiC); nmr τ 9.67 (m, 2), 9.25 (m, 3), and 8.85 (m, 6).

Preparation of 2- and 3-Pentyltrichlorosilane.—Using the procedure of Speier and Webster,[24] 37.6 g (74.2%) of 2- and 3-pentyltrichlorosilanes was prepared, bp 162–164° (lit. bp 165–168°[24]).

The 2- and 3-pentyltrichlorosilanes were methylated using 425 ml (1.275 mol) of 3 *M* methylmagnesium chloride. Distillation gave 5.71 g (22.7%) of 2- and 3-pentyltrimethylsilanes, bp 130–

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149°, n^{24}D 1.4187. These products were separated by preparative glpc using column B at 73°.

The 2-pentyltrimethylsilane (54%) gave the following spectra: ir 2900 (CH), 1460 (CH), 1400 ($SiCH_3$), 1250 ($SiCH_3$), and 850 cm^{-1} (SiC); nmr τ 10.16 (s, 9), 9.25 (m, 7), 8.82 (m, 4).

Anal. Calcd for $C_8H_{20}Si$: C, 66.58; H, 14.00. Found: C, 66.81; H, 13.78.

1-Bromo-2-pentyne.—1-Hydroxy-2-pentyne[25] (21.74 g, 0.258 mol), 100 ml of dry ether, and 4.3 ml of pyridine were allowed to react with 33 g (0.12 mol) of phosphorus tribromide using a published procedure.[25] Distillation under reduced pressure afforded 21.99 g (78.3%) of 1-bromo-2-pentyne, bp 77–80° (60 mm) [lit.[25] bp 147–148° (754 mm)].

1-Trimethylsilyl-2-pentyne.—1-Bromo-2-pentyne (10 g, 0.068 mol) in 25 ml of dry ether was added slowly to a mixture of 1.65 g (0.068 mol) of magnesium and 10 g (0.092 mol) of trimethylchlorosilane in 25 ml of dry ether. After refluxing for 3 hr, the reaction mixture was hydrolyzed and the ether layer was separated and dried over anhydrous magnesium sulfate. Distillation gave 0.95 g (14%) of 1-trimethylsilyl-2-pentyne.

The following spectra were obtained: ir (neat) 2960 and 2890 (CH), 220 (C≡C), 1455 (CH), 1400 ($SiCH_3$), 1250 ($SiCH_3$), 850 (SiC), and 695 cm^{-1} (SiC); nmr τ 10.21 (s, 9), 9.30 (t, 3), 9.00 (t, 2), 8.28 (m, 2).

***cis*- and *trans*-Trimethylsilyl-2-pentene.**—The trimethylsilylpentyne prepared above was dissolved in 25 ml of ethyl acetate and hydrogenated over platinum oxide at 20 psi initial pressure. Analysis by glpc on column A at 73° showed 11% *trans*-1-trimethylsilyl-2-pentene and 76% *cis*-1-trimethylsilyl-2-pentene.

***cis*- and *trans*-3-Penten-1-ol.**—Hydrogenation of 31.2 g (0.363 mol) of 3-pentyne-1-ol in 75 ml of methanol over platinum oxide yielded 23.9 g (75%) of crude 3-penten-1-ol (9% trans and 82% cis by glpc), bp 141–142° (753 mm) [lit.[26] bp 129.9° (628 mm)].

***cis*- and *trans*-1-Bromo-3-pentene.**—Using the procedure cited above, 20.7 g (0.23 mol) of the 3-penten-1-ol mixture was converted into the corresponding 1-bromo-3-pentenes with 6.43 g of pyridine and 9.2 ml (0.097 mol) of phosphorous tribromide. There was obtained 21.54 g (60%) of the product, bp 129° (750 mm), n^{20}D 1.4695 [lit.[26] bp 121.7° (621 mm), n^{20}D 1.4695]. Preparative glpc with column B yielded 18% of *trans*-1-bromo-3-pentene, ir (neat) 3000 (CH), 1650 (C=C), 960 (trans CH), and 635 cm^{-1} (CBr), and 70.8% of *cis*-1-bromo-3-pentene, ir (neat) 2950 (CH), 1650 (C=C), and a broad band from 720 to 550 cm^{-1} attributed to cis C–H bending and C–Br stretch.

***cis*- and *trans*-1-Trimethylsilyl-3-pentene.**—By the method described above for 1-trimethylsilyl-2-pentyne, 5.0 g (0.034 mol) of the 1-bromo-3-pentene mixture was converted into 1.46 g (30.7% yield) of 1-trimethylsilyl-3-pentenes, bp 68–72° (101 mm) [lit.[27] bp 139.8 (756.5 mm)]. The product, analyzed by glpc using column A, consisted of a trace of 1-trimethylsilylpentane, *trans*-1-trimethylsilyl-3-pentene (20%), and *cis*-1-trimethylsilyl-3-pentene (79%).

1-Trimethylsilyl-4-pentene.—The procedure described by Benkeser, Smith, and Noe[13] was followed to yield 3.19 g of product (33.6% yield).

***cis*- and *trans*-1-Trimethylsilylpentenes.**—These were prepared *via* the peroxide-catalyzed addition of trichlorosilane to 1-pentyne as described by Benkeser, *et al.*[11]

Addition of Methyldichlorosilane to 2-Pentyne.—2-Pentyne (10.0 g, 0.148 mol) and 10.9 g (0.148 mol) of methyldichlorosilane were allowed to react in cyclohexane as described previously for the pentadiene additions. There was obtained 10.71 g (39.6%) of methyldichlorosilylpentenes, bp 55–58° (90 mm).

Methylation with 3.2 *M* methylmagnesium chloride (0.16 mol) afforded 6.17 g (74.2%) of trimethylsilylpentenes, bp 71–73° (91 mm). The 2- and 3-trimethylsilyl-2-pentenes produced showed different glpc retention times than any of the pentadiene addition products.

Addition of Methyldichlorosilane to Excess Pentadienes in the Presence of a Chloroplatinic Acid Catalyst.—In a typical procedure, to a 100-ml three-necked flask equipped with an addition funnel, a thermometer (in the solution), and a Dry Ice–acetone condenser were added 10 ml (0.095 mol) of methyldichlorosilane, 15 ml (0.15 mol) of *trans*-1,3-pentadiene, 25 ml of cyclohexane, and three drops of 0.2 *M* chloroplatinic acid. The isomeric purity of the pentadiene was checked initially and after refluxing at 58° for 24 hr using glpc with column A at 25°. Before refluxing only *trans*-1,3-pentadiene was detected. After 24 hr of refluxing, the composition was again checked for the unreacted pentadiene. The mixture was then distilled under reduced pressure to give the methyldichlorosilylpentenes. See Table II.

Competition Reaction between *cis*- and *trans*-1,3-Pentadienes.—To a pressure flask 25 ml of cyclohexane, 2 drops of 0.2 *M* chloroplatinic acid, 10 ml (0.10 mol) of methyldichlorosilane, 6.8 g (0.1 mol) of *cis*-1,3-pentadiene, and 6.8 g (0.1 mol) of *trans*-1,3-pentadiene were added. The flask was sealed and heated at 91° for 24 hr. After cooling, the mixture was injected into the gas chromatograph using column A at 25°. Three peaks resulted. The one with the longest retention time was cyclohexane; the first or the one with the shortest retention time was *trans*-1,3-pentadiene (27.6 area %); the remaining peak was *cis*-1,3-pentadiene (72.4 area %). This same mixture was injected into a 0.5-in. diameter, 19-ft column (15% SE-30 on 30–60 mesh firebrick) at 110°. Three additional components were detected; the first was 38.2 area %, the second was 35.4 area %, and the last was 26.4 area % of the mixture of methyldichlorosilylpentenes. Vacuum distillation yielded 14.93 g (40.7%) of methyldichlorosilylpentene, bp 62–64° (14 mm).

The products were methylated using 75 ml (0.225 mol) of 3 *M* methylmagnesium chloride. Distillation afforded 8.83 g (75.9% yield) of products, bp 57–59° (41 mm). Four peaks resulted from glpc analysis and were identified as **3**, *trans*-2-trimethylsilyl-3-pentene (35.3%), **4**, *trans*-1-trimethylsilyl-2-pentene (1.9%), **2**, *cis*-1-trimethylsilyl-2-pentene (39.3%), and **5**, *cis*-1-trimethylsilyl-3-pentene (23.5%), by their retention times.

Registry No.—**1**, 763-21-3; **2**, 40762-94-5; **3**, 40762-95-6; **4**, 40795-28-6; **5**, 40762-96-7; methyldichlorosilane, 75-54-7; 1-pentyltrimethylsilane, 1641-49-2; 3-pentyltrimethylsilane, 40748-37-6; 2-pentyltrimethylsilane, 40748-38-7; 1-trimethylsilyl-2-pentyne, 40748-39-8; 1-bromo-2-pentyne, 16400-32-1.

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Bis(perfluoroalkylsulfonyl)methanes and Related Disulfones[1]

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Received March 26, 1973

The improved synthesis and chemistry of the acidic bis(perfluoroalkylsulfonyl)methanes, $R_fSO_2CH_2SO_2R_f$, and related disulfones are described. New substituted β-disulfones, *e.g.*, olefins, alcohols, and halo disulfones, are provided by various organometallic reactions, alkylations, and halogenations of the methylene disulfones or derivatives. Free-radical reactions of the bromo disulfones, $CF_3SO_2CBrXSO_2CF_3$ (X = Br and H), are also reported.

Bis(perfluoroalkylsulfonyl)methanes, $R_fSO_2CH_2SO_2R_f$ (R_f = CF_3 and C_8F_{17}), have been prepared by reaction of methylmagnesium halides with perfluoroalkanesulfonyl fluorides using diethyl ether as solvent.[2,3] Since these disclosures, however, very little information relating to the preparation and chemistry of these novel, acidic methylene disulfones and related β-disulfones has been reported. This paper describes an improved and convenient method for preparing disulfones from sulfonyl fluorides and the preparation of a variety of substituted β-disulfones by organometallic reactions, alkylations, and halogenations of the methylene disulfones or derivatives.

Results and Discussion

Improved Synthesis.—The bis(perfluoroalkylsulfonyl)methanes **1–3** were obtained in moderate to high yields by reaction of methylmagnesium chloride (or bromide) with sulfonyl fluorides using tetrahydrofuran as solvent (eq 1). The yield of bis(trifluoromethylsulfonyl)methane (**1**) was 75%, whereas yields of **2** and **3** ranged from 50 to 60%. Under similar conditions, the ethylidene disulfones **4–6** were obtained

$$2R_fSO_2F + 2RCH_2MgX \xrightarrow[25°]{THF} (R_fSO_2)_2CHR \quad (1)$$

X = Br, Cl; **1–7**

1, R = H; R_f = CF_3
2, R = H; R_f = C_4F_9
3, R = H; R_f = C_8F_{17}
4, R = CH_3; R_f = CF_3
5, R = CH_3; R_f = C_4F_9
6, R = CH_3; R_f = C_8F_{17}
7, R = C_6H_5; R_f = CF_3

from ethylmagnesium halides, as exemplified by the synthesis of 1,1-bis(trifluoromethylsulfonyl)ethane (**4**) in 80% yield by reaction of ethylmagnesium chloride with CF_3SO_2F. Reaction of benzylmagnesium chloride with CF_3SO_2F gave **7** in a lower yield of 40%.

All of the reactions are conveniently carried out at room temperature under atmospheric pressure. In general, the use of tetrahydrofuran affords much higher yields of disulfones than aliphatic ethers such as diethyl ether. In previous work[2,3] reactions of sulfonyl fluorides with methylmagnesium iodide in diethyl ether gave the methylene disulfones **1** and **3** in yields of about 10%.

Synthesis of **1–7** involves a sequence of reactions in which the corresponding monosulfone is one of the intermediates. In the proposed scheme (eq 2–6;

$$R_fSO_2F \xrightarrow{RCH_2MgX} R_fSO_2CH_2R + MgFX \quad (2)$$

$$R_fSO_2CH_2R \xrightarrow{RCH_2MgX} R_fSO_2CHRMgX + RCH_3 \quad (3)$$

$$R_fSO_2CHRMgX \xrightarrow{R_fSO_2F} R_fSO_2CHRSO_2R_f + MgFX \quad (4)$$

(6) H^+ ⇅ RCH_2MgX (5)

$$R_fSO_2C(MgX)RSO_2R_f$$

R = H, CH_3 or C_6H_5), the monosulfone is first formed by reaction of the sulfonyl fluoride with the Grignard reagent (eq 2). Transmetalation of the α hydrogen of the monosulfone with Grignard reagent occurs rapidly, giving $R_fSO_2CHRMgX$[4] (eq 3), which reacts with additional sulfonyl fluoride affording the disulfone, **1–7** (eq 4). Additional Grignard reagent is consumed in the process by the facile transmetalation of the α hydrogen of **1–7**, giving $R_fSO_2C(MgX)RSO_2R_f$ (eq 5) prior to the final hydrolysis step (eq 6). The higher yields of **1–7** were obtained by using 2–3 equiv of Grignard reagent. The properties of tetrahydrofuran apparently facilitate the transmetalation reactions and reaction 4 to afford higher yields of disulfones than obtained with aliphatic ethers such as diethyl and isopropyl ether. Tetrahydrofuran is known to be more basic than these ethers and more readily forms coordination complexes with organometallic compounds.[5,6]

The effect of the above solvents on the yield of disulfone and monosulfone is shown in Table I. In di-

TABLE I

SOLVENT EFFECTS

$$CF_3SO_2F + RCH_2MgCl \xrightarrow{solvent} CF_3SO_2CH_2R + (CF_3SO_2)_2CHR$$

R	Mole[a] ratio	Solvent	Yield, % Monosulfone	Yield, % Disulfone
H	1.5	Et_2O	12	11
H	3.0	Et_2O	70	7
H	3.0	THF	5	75
CH_3	2.0	THF		80
CH_3	2.0	Et_2O	15	60
CH_3	2.0	*i*-Pr_2O	38	45

[a] Ratio of Grignard reagent to CF_3SO_2F; the sulfonyl fluoride was added to a 3 *M* solution of Grignard reagent at room temperature. All reactions are exothermic.

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ethyl ether, a 3-mol ratio of methylmagnesium chloride to CF_3SO_2F gave the monosulfone, $CF_3SO_2CH_3$, as the major product. Under comparable conditions, use of THF afforded the disulfone, $CF_3SO_2CH_2SO_2CF_3$, in 75% yield. Similar results were obtained with ethylmagnesium chloride, but the solvent effect was less pronounced. The highest yield of the ethylidene disulfone, $CF_3SO_2CH(CH_3)SO_2CF_3$, was obtained in THF and the order of effectiveness was THF > diethyl ether > isopropyl ether.

Acidity.—Bis(trifluoromethylsulfonyl)methane, $CF_3SO_2CH_2SO_2CF_3$ (**1**), appears to be the strongest known carbon acid of the methylene series. It is a stronger acid than $CF_3SO_2CH_2SO_2C_6H_5$ ($pK_a = 5.1$[7]) or dinitromethane ($pK_a = 3.6$[8]) and carboxylic acids, *e.g.*, benzoic acid and salicylic acid. Comparison of the acidity of **1** and trifluoroacetic acid ($pK_a = 0.23$[9] and -0.26[10]) was examined. Attempts to obtain the ionization constant of **1** by conductivity measurements in water were unsuccessful because of its relatively low solubility (maximum concentration, 1 *M*) and very high degree of ionization. Consequently, **1** could not be distinguished from trifluoroacetic acid or trichloroacetic acid in aqueous media. The acidity of **1** and comparison with trifluoroacetic acid were initially obtained in terms of the Hammett acidity function, H_0, using known procedures.[11] The H_0 values for trifluoroacetic acid, **1**, and HCl (1 *M* solutions) using *p*-nitroaniline as the base indicator and methyl isobutyl ketone as solvent were 1.7, 1.0, and -0.6, respectively. The data suggest that **1** is a stronger acid than trifluoroacetic acid and the estimated pK_a is about -1.

The high acidity of **1** is believed to be due primarily to the very strong electron-withdrawing effect of the two CF_3SO_2 groups. The trifluoromethylsulfonyl group has been reported as one of the strongest electron-withdrawing groups known.[12] In general, the methylene disulfones **1–3** form stable, usually nonhygroscopic, salts by neutralization with metal carbonates or organic bases. Stable salts are also readily prepared from the ethylidene disulfones **4–6** and various other substituted disulfones described in this paper.

Organometallic Reactions.—Transmetalation of the methylene disulfones was found to occur rapidly and quantitatively at room temperature with methylmagnesium chloride in THF (eq 7). The reaction is

$$\underset{\mathbf{1\text{–}3}}{(R_fSO_2)_2CH_2} \xrightarrow[\text{THF, } 25^\circ]{CH_3MgCl} \underset{\begin{array}{l}\mathbf{8},\ R_f = CF_3\\ \mathbf{9},\ R_f = C_4F_9\\ \mathbf{10},\ R_f = C_8F_{17}\end{array}}{(R_fSO_2)_2CHMgCl} + CH_4 \qquad (7)$$

accompanied by evolution of an equivalent amount of methane. Under similar conditions, use of 2 equiv of methylmagnesium chloride resulted in transmetalation of both α hydrogens as indicated by the amount of methane produced.

Various substituted disulfones were obtained by reactions of the bis(perfluoroalkylsulfonyl)methylmagnesium chlorides **8–10** in THF with coreactants such as allyl halides, benzyl halides, chlorine, and bromine (Table II). The reported yields are based mainly on

TABLE II

ORGANOMETALLIC REACTIONS

$$(R_fSO_2)_2CHMgCl \xrightarrow[\text{THF}]{\text{coreactant}} \mathbf{11\text{–}17}$$

R_f	Coreactant	Product	Yield, %
CF_3	$CH_2{=}CHCH_2Br$	$(CF_3SO_2)_2CHCH_2CH{=}CH_2$ (**11**)	52
C_8F_{17}	$CH_2{=}CHCH_2Br$	$(C_8F_{17}SO_2)_2CHCH_2CH{=}CH_2$ (**12**)	40
CF_3	$C_6H_5CH_2Cl$	$(CF_3SO_2)_2CHCH_2C_6H_5$ (**13**)	35
CF_3	$\overline{CH_2CH_2O}$	$(CF_3SO_2)_2CHCH_2CH_2OH$ (**14**)	40
C_4F_9	$\overline{CH_2CH_2O}$	$(C_4F_9SO_2)_2CHCH_2CH_2OH$ (**15**)	50
CF_3	Br_2	$(CF_3SO_2)_2CHBr$ (**16**)	70
CF_3	Cl_2	$(CF_3SO_2)_2CHCl$ (**17**)	65

the use of 1 equiv of coreactant. A higher yield (80%) of the olefinic disulfone **11** was obtained by transmetalation of **1** with 2 equiv of methylmagnesium chloride and subsequent reaction with 2 equiv of allyl bromide.

Alkylations.—Reactions of silver bis(trifluoromethylsulfonyl)methane[3] (**18**) with organic halides were studied as routes to substituted disulfones. Aprotic solvents such as acetonitrile, methylene chloride, *p*-dioxane, and 1,2-dimethoxyethane (glyme) were used. In general, high conversions of **18** and formation of silver halide occurred with most of the halides, including simple halides such as *n*-butyl bromide. Satisfactory yields (20–60%) of the substituted disulfones were obtained only in the case of the more active organic halides, *e.g.*, allyl bromide and benzyl chloride, which afford the more stable carbonium ions (eq 8). A prominent side reaction which occurred in solvents other than glyme is the formation of **1** presumed to be due to abstraction of proton from the reaction media by the disulfone, carbanion, $(CF_3SO_2)_2CH^-$.

$$\underset{\mathbf{18}}{(CF_3SO_2)_2CHAg} + RX \xrightarrow{-AgX} (CF_3SO_2)_2CHR \qquad (8)$$

X = Br or Cl; **11**, R = $CH_2CH{=}CH_2$; **13**, R = $CH_2C_6H_5$

Alkylations in glyme afforded the ethylidene disulfone **4** instead of **1** as the major side product; similar results occurred using diglyme and tetraglyme. Reaction of *n*-butyl bromide with the silver salt **18** in glyme gave **4** in 75% yield accompanied by the formation of 1-butoxy-2-methoxyethane (**20**) (eq 9). The proposed intermediate in this reaction is the oxonium salt **19**, which can yield the products by dissociation and methylation of the disulfone carbanion.

$$\mathbf{18} \xrightarrow[CH_3OCH_2CH_2OCH_3]{n\text{-}C_4H_9Br} \underset{\mathbf{19}}{[CH_3OCH_2CH_2O(CH_3)C_4H_9]^+(CF_3SO_2)_2CH^-}$$

$$\mathbf{19} \longrightarrow \underset{\mathbf{4}}{(CF_3SO_2)_2CHCH_3} + \underset{\mathbf{20}}{CH_3OCH_2CH_2OC_4H_9} \qquad (9)$$

(7) L. M. Yagupolskii and N. V. Kondratenko, *Zh. Obshch. Khim.*, **33** (3), 920 (1963).

(8) "Methoden der Organischen Chemie, Metallorganishe Verbindungen" (Houben-Weyl), Vol 13 (1), Georg Thieme Verlag, Stuttgart, 1970, pp 35–64. A list of the acidities of about 115 carbon acids is given.

(9) W. Huber, "Titrations in Nonaqueous Solvents," Academic Press, New York, N. Y., 1967, pp 215 and 217.

(10) C. H. Rochester, "Acidity Functions," Academic Press, New York, N. Y., 1970, pp 39 and 65.

(11) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).

(12) W. A. Sheppard, *J. Amer. Chem. Soc.*, **85**, 1314 (1963).

α-Halo Disulfones.—Chlorination or bromination of the potassium salt of **1** in carbon tetrachloride afforded the corresponding monohalo disulfone **16** or **17** in yields of 70–90% (eq 10). These disulfones

$$(CF_3SO_2)_2CHK + X_2 \xrightarrow[CCl_4,\ 25°]{-KX} (CF_3SO_2)_2CHX \quad (10)$$
16, X = Br
17, X = Cl

are highly acidic and form thermally stable salts by neutralization with alkali metal carbonates. The dry silver and sodium salts of the bromo disulfone **16** were found to be stable up to 160 and 250°, respectively.

Halogenation of the potassium salts of **16** and **17** under similar conditions gave high yields of the *gem*-dihalo disulfones **21** and **22** (eq 11). Similarly, the α-haloethylidene disulfones **23** and **24** were obtained from the potassium salt of **4**. Bromination of the potassium salt of 4,4-bis(trifluoromethylsulfonyl)-butene-1 (**11**) also produced the olefinic bromo disulfone **25** in 62% yield. All of the halogenation reactions (eq 10 and 11) are rapid at room temperature and usually

$$(CF_3SO_2)_2CK \xrightarrow[CCl_4]{X_2} (CF_3SO_2)_2CX \quad (11)$$
(Y: K → X)
21, Y = X = Br
22, Y = X = Cl
23, Y = CH_3; X = Br
24, Y = CH_3; X = Cl
25, Y = $CH_2CH{=}CH_2$; X = Br

require only an equivalent amount of the halogenation agent.

Bis(trifluoromethylsulfonyl)dibromomethane (**21**) was also obtained in 59% yield by reaction of **1** with alkaline sodium hypobromite solution (eq 12).

$$(CF_3SO_2)_2CH_2 \xrightarrow[NaOH]{NaOBr} (CF_3SO_2)_2CBr_2 \quad (12)$$
21

Properties of the α-Bromo Disulfones.—The carbon–bromine bond of the α-bromo disulfones is indicated to be polarized so that the bromine is "positive" as in the case of N-halo compounds[13] and perfluoroalkyl iodides.[14] This property is due mainly to the very strong electron-withdrawing effect of the two CF_3SO_2

$$(CF_3SO_2)_2\overset{\delta^-}{C}\!-\!\overset{\delta^+}{Br}$$
|
Y

Y = H, CH_3, Br

groups. Removal of the bromine as an anion is difficult and under forcing conditions replacement of bromine with hydrogen usually results. Homolytic dissociation of the carbon–bromine bond, however, occurs readily and is initiated by light or free-radical catalysts.

The oxidizing property of the bromo disulfones is exemplified by the ease of reduction of the monobromo disulfone **16** with sodium iodide, yielding the sodium salt of **1**, iodine, and sodium bromide (eq 13).

$$\underset{\mathbf{16}}{(CF_3SO_2)_2CHBr} + 2NaI \xrightarrow[25°]{CH_3CN} (CF_3SO_2)_2CHNa + I_2 + NaBr \quad (13)$$

A comparison of the reactivity of **16** with bromo derivatives of other methylene compounds was of interest. Reaction of monobromodiethyl malonate with anhydrous sodium carbonate at 150° is reported to give a 55–70% yield of the tetraethyl ester of ethylenetetracarboxylic acid[15] (**26**) (eq 14). Under similar conditions, **16** gave only its sodium salt in high yield (eq 15).

$$2\ (C_2H_5O\overset{O}{\overset{\|}{C}})_2CHBr \xrightarrow[150°]{Na_2CO_3} \underset{\mathbf{26}}{(C_2H_5O\overset{O}{\overset{\|}{C}})_2C{=}C(\overset{O}{\overset{\|}{C}}OC_2H_5)_2} \quad (14)$$

$$\underset{\mathbf{16}}{(CF_3SO_2)_2CHBr} \xrightarrow[150°]{Na_2CO_3} (CF_3SO_2)_2CBrNa \quad (15)$$

Pyrolysis of salts of **16** further demonstrates the "positive" nature of the bromine atom. Decomposition of anhydrous $(CF_3SO_2)_2CBrK$ occurred exothermically at 240° to give CF_3Br, SO_2, and potassium fluoride as the major products.

Addition of the bromo disulfone **16** to terminally unsaturated olefins resulted when initiated by ultraviolet light or decomposing free-radical catalysts, *e.g.*, benzoyl peroxide or azobisisobutyronitrile (eq 16). The direction of addition, established by proton nmr, is the same as reported for perfluoroalkyl iodides.[16] In general, high conversions of **16** occurred to give 1:1 adducts and allylic bromination products, accompanied by the formation of **1**. With octene-1, the bromination side reaction occurred to the extent of about 40%, giving the methylene disulfone **1** and a mixture of bromooctene isomers (eq 17). The predominant bromooctene

$$\underset{\mathbf{16}}{(CF_3SO_2)_2CHBr} + CH_2{=}CHR \longrightarrow (CF_3SO_2)_2CHCH_2CHBrR \quad (16)$$
27, R = CH_2CH_2Cl; 70%
28, R = CH_2COOH; 50%
29, R = C_6H_{13}; 32%

$$\mathbf{16} + C_5H_{11}CH_2CH{=}CH_2 \longrightarrow (CF_3SO_2)_2CH_2 + \mathbf{30} \quad (17)$$
$$\mathbf{30} = \underset{\mathbf{30a}}{C_5H_{11}CHBrCH{=}CH_2} + \underset{\mathbf{30b}}{C_5H_{11}CH{=}CHCH_2Br}$$

isomer was **30b** formed by rearrangement of **30a** during the process; the ratio of isomers was 3:1.

The bromo disulfones were also found to be effective bromination agents for the side-chain bromination of aromatics. The most effective was bis(trifluoromethylsulfonyl)dibromomethane (**21**). Reaction of **21** with toluene in the presence of decomposing azobisisobutyronitrile yielded **1**, benzyl bromide, and benzal bromide (eq 18). A free-radical mechanism is suggested, since hydroquinone inhibits the reaction.

$$\underset{\mathbf{21}}{(CF_3SO_2)_2CBr_2} + PhCH_3 \xrightarrow[AIBN,\ 70°]{90\%} (CF_3SO_2)_2CH_2 + PhCH_2Br + PhCHBr_2 \quad (18)$$

Experimental Section

General.—The perfluoroalkanesulfonyl fluorides were obtained by electrochemical fluorination.[17-12] Perfluorooctanesulfonyl

(13) P. Kovacic, M. K. Lowery, and K. W. Field, *Chem. Rev.*, **70**, 639 (1970).

(14) R. E. Banks, "Fluorocarbons and Their Derivatives," Oldbourne Press, London, 1964, p 59.

(15) "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 273.

(16) G. Sosnovsky, "Free Radical Reactions in Preparative Organic Chemistry," Macmillan, New York, N. Y., 1965, p 36.

(17) T. J. Brice and P. W. Trott, U. S. Patent 2,732,398 (1956).

(18) J. Burdon, L. Farazmand, M. Stacey, and J. C. Tatlow, *J. Chem. Soc.*, 2574 (1957).

(19) T. Gramstad and R. N. Haszeldine, *J. Chem. Soc.*, 2640 (1957).

fluoride was purified by the method of Hansen.[20] Commercial Grignard reagents in THF or aliphatic ethers were generally used or were prepared by established methods.[21] All organometallic reactions were carried out under nitrogen. Reactions of trifluoromethanesulfonyl fluoride, bp −21°, were carried out under atmospheric pressure using a −78° condenser.

Infrared spectral data were obtained using a Perkin-Elmer 21 spectrophotometer. In most cases mineral oil mulls were used. A Varian Associates A-60 spectrometer was used for proton nmr with TMS as the internal standard and usually deuterated chloroform as solvent. All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected.

Bis(trifluoromethylsulfonyl)methane (1).—Procedures for the preparation of 1–7 are exemplified as follows. In a 3-l. flask fitted with a stirrer, gas inlet tube, thermometer, and a −78° condenser was placed 1 l. of a 3 *M* solution of methylmagnesium chloride in THF. Trifluoromethanesulfonyl fluoride (154 g, 1.0 mol) was bubbled into the stirred solution over a 1.5-hr period (exothermic) keeping the temperature at 35–50° (ice–water bath). After heating at 50–60° for 2.5 hr, the mixture was cooled and hydrolyzed by the slow addition[22] of 500 ml of 3 *N* HCl. The organic phase was separated and distilled to remove THF and the residue was stirred with 500 ml of 1 *N* HCl. Extraction with diethyl ether followed by distillation of the dry ether solution ($MgSO_4$) gave 106 g (76%) of **1**, bp 99–101° (25 mm). Recrystallization (CCl_4) gave mp 35° [lit.[3] bp 90° (15 mm); mp 35°]; nmr ($CDCl_3$) τ 5.01 (s, CH_2).

Bis(nonafluorobutylsulfonyl)methane (2).—Nonafluorobutanesulfonyl fluoride (60 g, 0.2 mol) was added to 200 ml of 3 *M* methylmagnesium chloride in THF. After hydrolysis and distillation of THF from the organic phase, 41.5 g of crude product, soluble in diethyl ether, was obtained. Sublimation *in vacuo* afforded 34.4 g (60%) of **2**, mp 85–90°. Recrystallization (CCl_4) gave 24.2 g, mp 99–100°, nmr (acetone) τ 4.30 (s, CH_2). In a similar reaction, using diethyl ether instead of THF as solvent, a 10% yield of **2** was obtained.

Anal. Calcd for $C_9H_2F_{18}O_4S_2$: C, 18.6; H, 0.3; F, 59.0. Found: C, 18.5; H, 0.4; F, 58.9.

Bis(heptadecafluorooctylsulfonyl)methane (3).—Methylmagnesium bromide (550 ml of a 3 *M* solution in diethyl ether) was added to a stirred mixture of 310 g of heptadecafluorooctanesulfonyl fluoride and 900 ml of THF. After hydrolysis, the organic phase was distilled to remove solvent and the residue was stirred with 400 ml of 10 *N* HCl at 80° (2 hr). The mixture was diluted with water and filtered to give 250 g of crude product. The dry solid mixture was stirred twice with anhydrous acetone (300 ml). Filtration gave 125 g of **3**, mp 161–165°. Recrystallization (ethyl acetate) gave mp 166–167° (lit.[2] mp 166–167°). The filtrate was evaporated and the solid was recrystallized (CCl_4) to give 60 g of **3**, mp 75–80°, having linear and branched heptadecafluorooctyl groups.[23] The above reaction was also carried out using only diethyl ether as solvent. The yield of **3** was about 15% and the major product was $C_8F_{17}SO_2CH_3$[2] (65%), mp 104–105°.

1,1-Bis(trifluoromethylsulfonyl)ethane (4).—Ethylmagnesium bromide was prepared by reaction of 286 g (2.6 mol) of ethyl bromide and 58 g (2.4 g-atoms) of magnesium in 950 ml of dry tetrahydrofuran. To the solution was added 243 g (1.6 mol) of trifluoromethanesulfonyl fluoride using procedures described for **1**. After hydrolysis and removal of THF from the organic phase, the crude product was dissolved in methylene chloride and the dry solution ($MgSO_4$) was distilled to give 185 g (79%) of **4**: bp 98–99° (20 mm); nmr ($CDCl_3$) τ 4.93 (m, 1, CH), 7.95 (d, 3, CH_3). Under similar conditions, reaction of the sulfonyl fluoride with ethylmagnesium chloride in THF gave **4** in 77% yield.

Anal. Calcd for $C_4H_4F_6O_4S_2$: C, 16.3; H, 1.4; F, 38.8. Found: C, 16.3; H, 1.3; F, 39.2.

The triethylamine salt of **4** was prepared by neutralization of **4** with triethylamine in diethyl ether. The insoluble product was heated at 70° *in vacuo* to afford the salt as a viscous liquid.

Anal. Calcd for $C_{10}H_{19}F_6NO_4S_2$: C, 30.4; H, 4.8; F, 28.8. Found: C, 30.3; H, 4.7; F, 28.8.

1,1-Bis(nonafluorobutylsulfonyl)ethane (5).—Nonafluorobutanesulfonyl fluoride (271 g, 0.9 mol) was added to ethylmagnesium bromide (1.2 mol) in 500 ml of THF. After hydrolysis, the organic phase was diluted with water. Filtration followed by recrystallization (CCl_4) gave 147 g of **5**, mp 83–84°.

Anal. Calcd for $C_{10}H_4F_{18}O_4S_2$: C, 20.2; H, 0.7; F, 57.6. Found: C, 20.2; H, 0.7; F, 57.6.

1,1-Bis(heptadecafluorooctylsulfonyl)ethane (6).—Ethylmagnesium bromide (0.5 mol) in 200 ml of diethyl ether was added to a stirred mixture of 150 g (0.3 mol) of $C_8F_{17}SO_2F$ and 200 ml of diethyl ether. After hydrolysis, the ether phase was filtered, giving 105 g of **6**, mp 152–157°. Recrystallization (FC-75[24]) gave mp 160–161°.

Anal. Calcd for $C_{18}H_4F_{34}O_4S_2$: C, 21.7; H, 0.4; F, 65.0. Found: C, 21.7; H, 0.4; F, 64.4.

Bis(trifluoromethylsulfonyl)phenylmethane (7).—Trifluoromethanesulfonyl fluoride (185 g, 1.3 mol) was bubbled into benzylmagnesium chloride (2.5 mol) in 900 ml of THF and 250 ml of diethyl ether. After hydrolysis, the organic phase was evaporated. The solid residue was stirred with water (2.5 l.) and neutralized with sodium hydroxide. The mixture was filtered, and the filtrate was acidified with HCl and then extracted with diethyl ether. Evaporation of the ether gave 92 g of crude **7**. Sublimation *in vacuo* gave 69 g of **7**, mp 100–102°. Recrystallization (hexane) afforded a high-purity sample melting at 101–101.5°.

Anal. Calcd for $C_9H_6F_6O_4S_2$: C, 30.4; H, 1.7; F, 32.0. Found: C, 30.5; H, 1.7; F, 31.8.

4,4-Bis(trifluoromethylsulfonyl)butene-1 (11).—To a stirred solution of 25 g (0.09 mol) of the methylene disulfone **1** in 125 ml of THF was added 83 ml of a 3.0 *M* solution of methylmagnesium chloride (0.25 mol) in THF (exothermic and methane evolved). To the solution was added 30.9 g (0.25 mol) of allyl bromide and the mixture was stirred under reflux for 1.5 hr. After cooling and hydrolysis (60 ml of 3 *N* HCl), the organic phase was separated and the major portion of solvent was removed by distillation. The residue was stirred with water and extracted with diethyl ether. Distillation of the dry etherate ($MgSO_4$) gave 22.4 g (79%) of **11**: bp 102–104° (24 mm); nmr ($CDCl_3$) τ 5.08 (t, 1, CH), 6.77 (t, 2, $CH_2CH{=}CH_2$), 4.1 (m, 1, $CH{=}CH_2$), 4.6 (m, 2, $CH{=}CH_2$); ir 6.05 μ (C=C).

Anal. Calcd for $C_6H_6F_6O_4S_2$: C, 22.5; H, 1.9; F, 35.6. Found: C, 21.7; H, 1.7; F, 36.1.

4,4-Bis(heptadecafluorooctylsulfonyl)butene-1 (12).—Allyl bromide (5.1 g, 0.04 mol) was added to a solution of **10** prepared by reaction of methylmagnesium chloride (0.04 mol) in tetrahydrofuran with a stirred suspension of 25 g (0.03 mol) of the methylene disulfone **3** in 125 ml of tetrahydrofuran. The resultant solution was stirred at 60° for 1 hr and hydrolyzed with 25 ml of 3 *N* HCl, and 250 ml of H_2O was added. The organic phase was separated and diluted with 250 ml of H_2O. Filtration gave 25 g of solid. Recrystallization ($CHCl_3$) gave 13 g of impure **12**, mp 85–104°. Extraction with $CF_2ClCFCl_2$ followed by evaporation of the solvent gave 8.7 g: mp 85–86.5°; nmr ($CF_2ClCFCl_2$) τ 5.05 (t, 1, CH), 6.76 (t, 2, $CH_2CH{=}CH_2$), 3.5–4.9 (m, 3, $-CH{=}CH_2$).

Anal. Calcd for $C_{20}H_6F_{34}O_4S_2$: C, 23.5; H, 0.6; F, 63.3. Found: C, 23.4; H, 0.8; F, 62.6.

1,1-Bis(trifluoromethylsulfonyl)-2-phenylethane (13).—Methylmagnesium chloride (0.15 mol) in 50 ml of THF was added to 25 g (0.09 mol) of **1** in 125 ml of THF. To the solution was added 19 g (0.15 mol) of distilled benzyl chloride and the mixture was stirred at 60° for 1 hr. Procedures for the isolation of **13** were the same as described for **11**. Distillation gave 9.5 g of **13**: bp 71–72° (0.05 mm); mp 38–39°; nmr ($CDCl_3$) τ 4.90 (t, 1, CH), 6.20 (d, 2, CH_2), 2.65 (m, 5, aromatic).

Anal. Calcd for $C_{10}H_8F_6O_4S_2$: C, 32.4; H, 2.2; F, 30.8. Found: C, 32.2; H, 2.3; F, 30.9.

3,3-Bis(trifluoromethylsulfonyl)propan-1-ol (14).—The procedures described for **11** were used. Ethylene oxide (4.8 g, 0.11 mol) was added to a cooled solution (5°) of **8** prepared by reaction of methylmagnesium bromide (0.05 mol) in diethyl ether with 10 g (0.04 mol) of **1** in 100 ml of THF (−78° condenser). The mixture was allowed to warm to 25° and stirred for 1.5 hr. After hydrolysis and extraction with diethyl ether, distillation gave 6.4 g of **1** and 1.6 g of **14**: bp 112° (5 mm); nmr ($CDCl_3$) τ

(20) R. L. Hansen, U. S. Patent 3,346,612 (1967).

(21) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Englewood Cliffs, N. J., 1954.

(22) Addition of the first 5-ml portion of 3 *N* HCl should be carried out with caution, since the initial reaction is vigorous and methane is evolved from unreacted methyl Grignard.

(23) The starting sulfonyl fluoride contained about 80% linear and 20% branched perfluorooctyl groups.

(24) FC-75 is a commercial inert fluorochemical available from the 3M Co.

4.50 (t, 1, CH), 7.30 (m, 2, CH_2CH_2OH), 6.08 (m, 2, CH_2CH_2OH), and 7.60 (s, 1, OH).

3,3-Bis(nonafluorobutylsulfonyl)propan-1-ol (15).—Ethylene oxide (7.4 g, 0.17 mol) was added to a cooled solution (5°) of **9**, prepared by reaction of methylmagnesium chloride (0.06 mol) in tetrahydrofuran and 21.5 g (0.04 mol) of the disulfone **2** in 125 ml of tetrahydrofuran. The mixture was stirred at 60° for 1 hr. After hydrolysis and extraction with diethyl ether, evaporation of the organic phase gave 24 g of a semisolid. The solid was washed with water and dissolved in hot butyl chloride. Cooling to 0° and filtration gave 5 g of **2**, and evaporation of the filtrate gave 10 g of **15**. Recrystallization (CCl_4) gave mp 58–60°; nmr ($CF_2ClCFCl_2$) τ 4.31 (t, 1, CH), 7.26 (t, 2, CH_2CH_2OH), 6.09 (m, 2, CH_2CH_2OH), 8.06 (s, 1, OH).

Anal. Calcd for $C_{11}H_6F_{18}O_5S_2$: C, 21.2; H, 1.0; F, 54.8. Found: C, 21.0; H, 1.0; F, 55.0.

Preparation of Salts.—The general procedure for preparation of the potassium and silver salts of the various acidic disulfones involved neutralization of the acid with the corresponding carbonate in methanol followed by filtration, evaporation of the filtrate, and drying of the salt at 70–100° *in vacuo*. The syntheses of the sodium and silver salts of **1** in aqueous media were reported previously.[3]

Organic salts were also prepared from **1** and other acidic disulfones by neutralization in diethyl ether or methanol. As an example, neutralization of 50 g of **1** in diethyl ether with 15.8 g of morpholine gave 54.6 g of the insoluble salt, which was purified by washing with diethyl ether and drying *in vacuo*, mp 99.5–101.5°.

Anal. Calcd for $C_7H_{11}F_6NO_5S_2$: C, 22.9; N, 3.8; H, 3.0. Found: C, 22.9; N, 3.9; H, 2.9; H_2O, 0.08.

Other organic salts of **1** were prepared from diethylamine (mp 101–102.5°), *N*-methylaniline (mp 105–107°), piperidine (mp 68–70°), and guanidine (mp 112–114°).

Alkylations.—The reaction of silver bis(trifluoromethylsulfonyl)methane (**18**) with allyl bromide in *p*-dioxane exemplifies the procedures used. Allyl bromide (12.1 g, 0.1 mol) was added slowly to a stirred solution of 38.7 g (0.1 mol) of dry **18** in 50 ml of spectrograde *p*-dioxane (exothermic). The mixture was stirred in the dark at 25° for 1 hr and under reflux for 4 hr. Filtration and distillation of the filtrate gave 24.1 g, bp 65–67° (4 mm). Glc[25] indicated a 2.6:1 mixture of 4,4-bis(trifluoromethylsulfonyl)butene-1 (**11**) and **1** (yield of **11**, 52%). Yields of **11** using other solvents are as follows: glyme (30%), methylene chloride (40%), and acetonitrile (20%).

Bis(trifluoromethylsulfonyl)bromomethane (16).—To a suspension of 54 g (0.17 mol) of the neutral and dry potassium salt of **1** in 225 ml of carbon tetrachloride was added 27.6 g (0.17 mol) of bromine in 30 ml of carbon tetrachloride. The mixture was stirred at 25° until the bromine color disappeared. Filtration followed by distillation of the filtrate gave 56.5 g (91%) of **16**, bp 93–94.5° (9 mm), nmr ($CDCl_3$) τ 3.77 (s, CH).

Anal. Calcd for $C_3HBrF_6O_4S_2$: C, 10.0; Br, 22.3; F, 31.7. Found: C, 9.9; Br, 22.4; F, 31.5.

In experiments using the potassium salt of **1**, containing small amounts of K_2CO_3, **16** contaminated with the dibromide **21** was obtained. Purification was carried out by neutralization of the mixture with K_2CO_3 (methanol), washing the dry salt with CCl_4 to remove **21**, followed by acidification of the salt and redistillation.

The sodium salt of **16** was prepared by neutralization of the acid with Na_2CO_3 (methanol). The salt was azeotropically dried with benzene and then *in vacuo* at 80°, mp 254–256° dec.

Anal. Calcd for $C_3BrF_6O_4S_2Na$: C, 9.5; Br, 21.0; F, 29.9; Na, 6.0. Found: C, 9.7; Br, 20.9; F, 29.8; Na, 5.8.

Bis(trifluoromethylsulfonyl)chloromethane (17).—To a suspension of 25 g (0.08 mol) of the potassium salt of **1** in 250 ml of CCl_4 was added 5.5 g (0.08 mol) of chlorine (exothermic). The mixture was stirred at 25° for 2 hr. Filtration followed by distillation of the filtrate gave 19.2 g of **17**, bp 84–86° (18 mm), nmr ($CDCl_3$) τ 3.83 (s, CH), containing a small amount of **22**.

Anal. Calcd for $C_3HClF_6O_4S_2$: C, 11.5; Cl, 11.3; H, 0.3. Found: C, 11.2; Cl, 13.2; H, 0.2.

Bis(trifluoromethylsulfonyl)dibromomethane (21).—Bromine (5.8 g) was added to a solution of 4.3 g of sodium hydroxide in 50 ml of H_2O, cooled to 0°. A solution, prepared from 5.0 g (0.02 mol) of the methylene disulfone **1**, 2.5 g of sodium hydroxide, and 25 ml of H_2O, was added to the stirred sodium hypobromite solution. The mixture was stirred at 25° for 63 hr and filtered and the filtrate was acidified with 3 *N* HCl. The mixture was extracted with methylene chloride, and the extract was shaken with 5% Na_2CO_3, dried ($MgSO_4$), and distilled, giving 3.7 g of **21**, bp 107–108° (17 mm).

Anal. Calcd for $C_3Br_2F_6O_4S_2$: C, 8.2; Br, 36.5; F, 26.0; mol wt, 438. Found: C, 8.6; Br, 37.1; F, 26.5; mol wt ($CHCl_3$), 432.

The compound was also prepared in 79% yield by bromination of the potassium salt of the monobromo disulfone **16** in CCl_4.

Bis(trifluoromethylsulfonyl)dichloromethane (22).—The compound was obtained in 80% yield by chlorination of the potassium salt of the monochloro disulfone **17** using procedures described for **17**. **22** had bp 95.0–95.5° (40 mm).

Anal. Calcd for $C_3Cl_2F_6O_4S_2$: C, 10.3; Cl, 20.3. Found: C, 10.4; Cl, 19.7.

1,1-Bis(trifluoromethylsulfonyl)-1-bromoethane (23).—Bromination of the potassium salt of the ethylidene disulfone **4** in CCl_4 gave **23** (83%), bp 89–90° (10 mm).

Anal. Calcd for $C_4H_3BrF_6O_4S_2$: C, 12.9; Br, 21.4; F, 30.6. Found: C, 12.9; Br, 21.2; F, 30.9.

4,4-Bis(trifluoromethylsulfonyl)-4-bromobutene-1 (25).—Using procedures described for **16**, bromination of 6 g (0.02 mol) of the dry potassium salt of the olefinic disulfone **11** with 2.7 g (0.02 mol) of bromine gave 4.9 g of **25**: bp 85–88° (5 mm); nmr ($CDCl_3$) τ 6.44 (d, 2, CH_2), 3.5–4.8 (m, 3, $CH{=}CH_2$); ir (neat) 6.08 μ (w, C=C).

Anal. Calcd for $C_6H_5BrF_6O_4S_2$: C, 18.1; Br, 20.0; F, 28.6. Found: C, 17.9; Br, 20.8; F, 28.3.

1,1-Bis(trifluoromethylsulfonyl)-3-bromo-5-chloropentane (27).—A mixture of 10 g (0.03 mol) of bis(trifluoromethylsulfonyl)bromomethane (**16**), 3.6 g (0.04 mol) of 4-chlorobutene-1, and 6 ml of methylene chloride (quartz flask) was irradiated at 25° for 4.0 hr using a 140-W Hanovia ultraviolet lamp. Distillation gave 8.8 g (70%) of **27**: bp 93–94° (0.05 mm); nmr ($CDCl_3$) τ 4.53 (m, 1, $CHCH_2$), 5.47 (m, 1, CHBr), 6.25 (t, 2, CH_2Cl), 7.10 (m, 2, $CHCH_2CHBr$), and 7.66 (q, 2, CH_2CH_2Cl, J = 6.0 Hz).

Anal. Calcd for $C_7H_8BrClF_6O_4S_2$: C, 18.7; Br, 17.8; F, 25.4. Found: C, 18.7; Br, 17.2; F, 25.4.

5,5-Bis(trifluoromethylsulfonyl)-3-bromovaleric Acid (28).—Using procedures described for the preparation of **27**, a mixture of 10 g (0.04 mol) of **16**, 3.5 g (0.04 mol) of 3-butenoic acid, and 6 ml of methylene chloride was irradiated for 6 hr. Filtration gave 6.0 g of **28**, mp 147–149°. Recrystallization ($CHCl_3$) gave mp 146.5–147.5°; nmr (CD_3CN) τ 4.17 (broad, 1, $CHCH_2$), 5.46 (m, 1, CHBr), 6.91 (m, complex, 4, $CH_2CHBrCH_2COOH$), 2.34 (s, 1, COOH).

Anal. Calcd for $C_7H_7BrF_6O_6S_2$: C, 18.9; H, 1.6; F, 25.6; neut equiv, 445.2 and 222.6. Found: C, 19.1; H, 1.8; F, 25.7; neut equiv, 468 and 225.

1,1-Bis(trifluoromethylsulfonyl)-3-bromononane (29).—The procedure described for **27** was used. Photolysis of 10 g (0.03 mol) of **16** and 3.5 g (0.03 mol) of distilled octene-1 followed by distillation gave 4.5 g of **29**: bp 97–98° (0.1 mm); nmr ($CDCl_3$) τ 4.48 (m, 1, $CHCH_2$), 5.72 (m, 1, CHBr), 7.17 (m, 2, $CHCH_2CHBr$), 8.10 (broad, 2, $CHBrCH_2CH_2$), 8.63 (broad, 8, $(CH_2)_4CH_3$, and 9.10 (t, 3, CH_3).

Anal. Calcd for $C_{11}H_{17}BrF_6O_4S_2$: C, 28.0; H, 3.6; Br, 17.0; F, 24.2. Found: C, 28.9; H, 3.6; Br, 16.2; F, 24.2.

The above distillation also gave a fraction, bp 94° (25 mm) to 77° (0.3 mm), which separated into two liquid phases. The lower phase (3.8 g) was **1** and the upper phase (1.5 g) after washing with 5% Na_2CO_3 was a mixture of bromooctenes **30a** and **30b** identified by ir and nmr.

Bromination of Toluene.—A mixture of 11.0 g (0.025 mol) of the dibromo disulfone **21**, 4.6 g (0.05 mol) of toluene, and 0.4 g of azobisisobutyronitrile was stirred at 75° for 20 hr. Distillation gave 0.7 g of toluene and 11.6 g of distillate, bp 85–89° (30 mm). The distillate (two phases) was separated and the upper phase was washed with 5% K_2CO_3 to give 4.9 g of benzyl bromide identified by infrared and nmr spectroscopy. The lower phase was mainly **1** (6.7 g). Distillation also afforded 1.5 g of benzal bromide, bp 65–67° (0.5 mm).

The above reaction of **21** and toluene was repeated using 0.3 g of hydroquinone instead of the azo catalyst; no appreciable reaction occurred at 80° (45 hr).

(25) A 6 ft × 0.12 in. column (98°) composed of 10% SE-30 on 80–100 mesh "S" stainless was used. The injection port was at 180°.

Acknowledgment.—The authors thank Dr. J. J. McBrady for interpretations of the infrared and nuclear magnetic resonance spectra, Messrs. P. B. Olson and J. G. Gagnon for the elemental analyses, Messrs. S. W. Bany, D. P. Wilmes, and A. H. Stoskopf for technical assistance, Dr. J. W. Belisle for acidity measurements, and Dr. T. J. Brice for his many helpful suggestions during the course of this work.

Registry No.—**1**, 428-76-2; **1** potassium salt, 33249-12-6; **1** morpholine salt, 31322-96-1; **1** diethylamine salt, 40906-76-1; **1** *N*-methylanilme salt, 40906-77-2; **1** piperidine salt, 31323-01-0; **1** guanidine salt, 31322-97-1; **2**, 29214-37-7; **3**, 29214-34-4; **4**, 31253-33-5; **4** triethylamine salt, 40906-78-3; **4** potassium salt, 40906-79-4; **5**, 40906-80-7; **6**, 40906-81-8; **7**, 40906-82-9; **8**, 40906-83-0; **9**, 40906-84-1; **10**, 40906-85-2; **11**, 30354-36-0; **11** potassium salt, 40906-86-3; **12**, 29214-36-6; **13**, 31139-48-7; **14**, 30354-37-1; **15**, 29269-32-7; **16**, 30354-38-2; **16** sodium salt, 30354-42-8; **16** potassium salt, 30354-43-9; **17**, 29214-39-9; **17** potassium salt, 40906-87-4; **18**, 31322-84-6; **21**, 40906-88-5; **22**, 40906-89-6; **23**, 40906-90-9; **25**, 40906-91-0; **27**, 30354-40-6; **28**, 30416-82-1; **29**, 30354-41-7; **30a**, 40906-92-1; **30b**, 25466-54-0; methylmagnesium chloride, 676-58-4; trifluoromethanesulfonyl fluoride, 335-05-7; nonafluorobutanesulfonyl fluoride, 375-72-4; methylmagnesium bromide, 75-16-1; heptadecafluorooctanesulfonyl fluoride, 307-35-7; ethylmagnesium bromide, 925-90-6; benzylmagnesium chloride, 6921-34-2; allyl bromide, 106-95-6; benzyl chloride, 100-44-7; ethylene oxide, 75-21-8; bromine, 7726-95-6; chlorine, 7782-50-5; 4-chlorobutene-1, 927-73-1; 3-butenoic acid, 625-38-7; octene-1, 111-66-0; toluene, 108-88-3; benzyl bromide, 100-39-0; benzal bromide, 618-32-6.

Mechanisms of Elimination Reactions. XIX. Rates and Product Proportions in the Reactions of 2-Methyl-2-butyl Halides with Thiolate Ions[1]

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Received June 7, 1973

Rates of reaction of 2-chloro-2-methylbutane with various thiolates have been determined in ethyl, isopropyl, and *tert*-butyl alcohols. The proportions of 2-methyl-1-butene and 2-methyl-2-butene in the products have been determined under the same conditions. Some experiments have also been done with 2-iodo- and 2-bromo-2-methylbutane, and with alkoxide, phenoxide, and phenylselenoxide bases. The elimination is faster with the sulfur than with the oxygen bases. The Brønsted β values for the reaction of substituted thiophenoxides with 2-methyl-2-butyl chloride run 0.13 to 0.16, reflecting a low sensitivity of rate to pK_b. The orientation also is little affected by changes in the basicity or steric requirements of the thiolates, showing a strong preference for the Saytzev-rule product in all cases. The nature of the transition state for elimination is discussed in the light of these results.

A problem of long standing in discussions of the effect of the nature of the base on rates and product proportions in eliminations is that the base is usually the conjugate base of the solvent. A change in base thus entails a change in solvent as well. If the base is changed without changing the solvent, the possibility remains that conjugate base of the solvent, in equilibrium with the added base, will be the actual reactant. Only when the added base is much weaker than the conjugate base of the solvent is this problem minimized.

Because thiolates are much weaker bases than the corresponding alkoxides or phenoxides, and because thiolates are reported to react more rapidly than alkoxides with tertiary alkyl halides,[3,4] we chose the reaction of thiolates with 2-methyl-2-butyl halides in alcoholic media as a means of studying steric and electronic effects of the base on rates and product proportions in eliminations from 2-methyl-2-butyl halides. Observed rate constants are recorded in Table I. To the rate constants used in the Brønsted correlations (see below), a small correction for accompanying solvolysis was applied where necessary.[5] The corrected values are given in Table II. The proportions of 2-methyl-1-butene in the olefinic products were determined by glpc and are recorded in Table III. No correction for solvolysis is necessary. The solvolysis gives primarily substitution product, and control experiments showed that the olefin composition is not affected by changing the thiolate concentration.

The low sensitivity of the relative yields of 2-methyl-1-butene and 2-methyl-2-butene (Table III) to the nature of the thiolate indicates a rather loose transition state, in which the base has not interacted strongly enough with the substrate for differences in base strength to have an appreciable effect. Particularly striking is the apparent absence of any steric effect along the series *n*-BuSH, *sec*-BuSH, *t*-BuSH. Although few other examples of variation of base without concomitant variation of solvent are known, it is certainly not true that orientation is generally insensitive to the nature of the base under such circumstances. The phenoxide gives substantially more 1-ene than the thiophenoxide (Table III), and substituted phenoxides with 2-butyl tosylate give a decrease in 1-ene with decreasing basicity of the phenoxide.[6] A slight trend in the same direction is noted with the substituted thiophenoxides in the present work, but the variation is barely outside experimental error.

There is somewhat more variation of product proportions with change of solvent and leaving group. While results in ethyl and isopropyl alcohols are similar, there is a marked increase in 1-ene and decrease in rate in *tert*-butyl alcohol. Perhaps the base is less hydrogen bonded, and therefore stronger, in *tert*-butyl than in

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TABLE I

OBSERVED RATE CONSTANTS FOR REACTIONS OF 2-CHLORO-2-METHYLBUTANE[a]

Registry no.	Base	Temp, °C	$k_2 \times 10^5$, l. mol^{-1} sec^{-1}, in EtOH	in *i*-PrOH	in *t*-BuOH
26385-25-1	*n*-BuSK	35.2	7.55 ± 0.23		2.49 ± 0.12
	n-BuSK	55.2	74.1 ± 0.8	62.4 ± 0.9	11.9 ± 0.0
40973-65-7	*sec*-BuSK	55.2	71.5 ± 1.7		
10577-48-7	*t*-BuSK	55.2	64.4 ± 1.5		
3111-52-2	C_6H_5SK	35.2	5.97 ± 0.28	5.26 ± 0.09	
	C_6H_5SK	55.2	60.4 ± 0.5	40.6 ± 0.03	
31367-69-8	*p*-MeC_6H_4SK	55.2	64.3 ± 1.5	47.1 ± 1.0	11.9 ± 0.3
40645-42-9	*p*-ClC_6H_4SK	55.2	41.8 ± 2.3	28.0 ± 0.1	8.83 ± 0.08
40973-68-0	*m*-ClC_6H_4SK	55.2	38.5 ± 0.2		
40973-69-1	*p*-BrC_6H_4SK	55.2			8.34 ± 0.09
40973-70-4	*p*-$MeCOC_6H_4SK$	55.2	26.4 ± 0.4	19.8 ± 1.6	
	ROK	35.2	0.619 ± 0.027	0.239 ± 0.014	
	ROK	55.2	9.80 ± 0.05		0.57 ± 0.10
1192-96-7	*p*-MeC_6H_4OK	55.2	13.0 ± 0.70		0.51 ± 0.10
40973-72-6	C_6H_5SeK	55.2	89.0		
	Solvolysis	55.2	0.826 ± 0.027	0.173 ± 0.012	
	Solvolysis	60.5	1.35	0.272	
	n-BuSK	35.2			248[b]
	n-BuSK	35.2			2070[c]

[a] Each figure is the average of two to five runs, with indicated average deviation. The figure is for a single run where no deviation is listed. [b] For 2-bromo-2-methylbutane. [c] For 2-iodo-2-methylbutane.

TABLE II

RATE CONSTANTS FOR REACTIONS OF 2-CHLORO-2-METHYLBUTANE AT 55.2°, CORRECTED FOR SOLVOLYSIS[a]

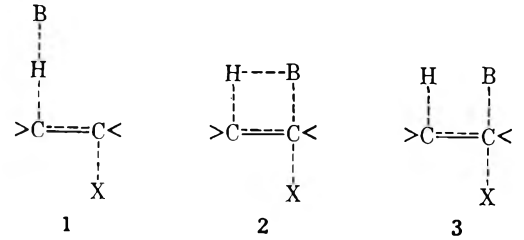
Base	$k_2 \times 10^5$, l. mol^{-1} sec^{-1}, in EtOH	in *i*-PrOH	in *t*-BuOH
p-MeC_6H_4SK	60.0	46.2	11.9
C_6H_5SK	56.5	39.7	
p-ClC_6H_4SK	37.3	27.1	8.83
m-ClC_6H_4SK	33.9		
p-BrC_6H_4SK			8.34
p-$MeCOC_6H_4SK$	21.9	18.9	

[a] Corrected by the method of McLennan: D. J. McLennan, *J. Chem. Soc. B*, 705 (1966).

ethyl or isopropyl alcohol. While this might explain the change in orientation, it is difficult to see why a stronger base would react at a slower rate. The decrease in rate may indicate conversion of the base to a less reactive, ion-paired form in *tert*-butyl alcohol. In contrast to the present results, 2-phenylethyl halides react faster in *tert*-butyl alcohol.[7,8] Different blends of solvent and base properties must be involved in the two cases. The Hughes–Ingold qualitative theory of solvent effects would predict a faster reaction in a less polar solvent,[9,10] again in contrast to the present results.

The decrease in per cent 1-ene along the series Cl > Br > I is indicative of increasing double-bond character of the transition state with increasing leaving-group ability of the halogen, as noted before with oxygen bases.[11,12] This leaving-group effect, and the other orientation data we have discussed above, are all consistent with the variable transition state theory of the E2 reaction.[13–15] In the framework of this theory, the transition state would be one with a great deal of double-bond character, and loose bonds between the leaving group and the α carbon, the β hydrogen, and the β carbon, and the β hydrogen and the base.

More recently, a different form of the variable transition state theory has been suggested, in which it is considered that the transition state ranges from E2H (1) to E2C (3).[16–21] Eliminations promoted by halide



1 2 3

ions in acetone and by thiolate ions in alcohol are proposed to have transition states near the E2C end of the spectrum.

The thiolate-promoted eliminations fit well into either the conventional variable transition state theory or the E2H–E2C theory, for both can accommodate a loose transition state with high double-bond character. An E2C-like transition state, with its interaction between

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TABLE III

OLEFIN COMPOSITIONS FOR ELIMINATIONS FROM 2-CHLORO-2-METHYLBUTANE

Base	Temp, °C	% 1-ene[a] in EtOH	% 1-ene[a] in i-PrOH	% 1-ene[a] in t-BuOH
n-BuSK	35.2	25.0 ± 0.7		27.7 ± 0.3
	55	25.5 ± 1.0	26.2 ± 0.5	31.2
	85	30		33.7 ± 0.4
sec-BuSK	55	26.9 ± 0.5		
t-BuSK	35	24.6		28.3 ± 0.5
	55	27.9 ± 0.6		31.2
	85	30		34.2 ± 0.6
p-MeC_6H_4SK	55	28.9 ± 0.5	28.5 ± 0.5	33.4 ± 0.5
	85	32.0	32.4 ± 1.0	37.5 ± 1.0
	110		34.0 ± 0.5	
C_6H_5SK[d]	35	29.0 ± 0.4		30.0 ± 0.2
	55	29.4 ± 0.2	28.5 ± 0.5	32.2 ± 0.3
	85	31.4 ± 0.3		
	110	33.7 ± 0.7		
p-ClC_6H_4SK	55	27.2 ± 0.2	27.2 ± 0.5	30.8 ± 0.4
	85	30.6 ± 0.3		36.6 ± 2.0
p-$MeCOC_6H_4SK$	55	27.0 ± 0.5	26.5 ± 0.5	
C_6H_5OK[e]	55			45.0
	85	39		
C_6H_5SeK	55	27.4		
	85	29.0		
n-BuSK	55			25.6[b]
	35			20.8[c]
t-BuSK	55			25.7[b]
	85			27.5[b]
	35			20.7[c]

[a] Out of total olefin (2-methyl-1-butene + 2-methyl-2-butene). Deviations are average deviations from the average of two to six runs. The figure is for a single run where no deviation is listed. [b] For 2-bromo-2-methylbutane. [c] For 2-iodo-2-methylbutane. [d] W. H. Saunders, Jr., S. R. Fahrenholtz, E. A. Caress, J. P. Lowe, and M. Schreiber, *J. Amer. Chem. Soc.*, **87**, 3401 (1965), gives 32% 1-ene at reflux and G. Biale, D. Cook, D. J. Lloyd, A. J. Parker, I. D. R. Stevens, J. Takahashi, and S. Winstein, *J. Amer. Chem. Soc.*, **93**, 4735 (1971), gives 29.5% at 50° in ethanol. R. A. Bartsch and J. F. Bunnett, *J. Amer. Chem. Soc.*, **90**, 408 (1968), also report 26% 1-ene from 2-bromo-2-methylbutane in ethanol. [e] Part of the reaction with "C_6H_5OK" may involve the conjugate base of the solvent. While a 10% excess of phenol was used to suppress solvent ionization, the conjugate base of the solvent may be sufficiently reactive to compete even in very small concentration.

the base and the α carbon, affords a reasonable explanation of the high effectiveness of the weakly basic but strongly nucleophilic thiolates relative to the much more strongly basic alkoxide. Otherwise, there is nothing in the present results that compels either the acceptance or rejection of the E2C mechanism for the reaction of tertiary alkyl halides with thiolates.

More recently, it has been suggested that E2C reactions and other second-order eliminations from readily ionizable substrates may occur *via* attack of base on an ion pair derived from the substrate.[22,23] It seems difficult to reconcile such a mechanism with the dependence of orientation on leaving group, which is qualitatively the same as that observed for the reaction of alkoxides with secondary halides,[11,12] a reaction which is almost certainly E2. That the anion in an ion pair would have much effect at all on the susceptibility of the various β hydrogens of the cation to attack by base, let alone the same effect as in E2 reactions, appears *a priori* improbable. Evidence on whether the leaving group affects orientation in E1 reactions would be relevant to the ion-pair hypothesis, for many examples of the E1 reaction doubtless involve attack of solvent or counterion on a β hydrogen of the cation in an ion pair. A recent study has shown that the proportion of 2-pentene (out of total pentenes) from ethanolysis of 2-pentyl derivatives remains constant at 94% for the leaving groups Br, SMe_2Br, SMe_2I, and NMe_3I, though there is a curious decrease to 87% for SMe_2ClO_4.[24] Except for the last substrate, which differs from the others in having a totally nonnucleophilic anion, the data support the belief that the leaving group should have little or no effect on orientation in E1 reactions. In the ion-pair mechanism, where the more reactive alkoxide or thiolate ion is supposed to attack the ion pair, even less discrimination would be expected. While the evidence is not sufficiently comprehensive for a definitive conclusion, we consider it improbable that our reactions occur *via* the ion-pair mechanism.

The insensitivity of the rates to the structure and strength of the thiolate bases confirms our conclusion that the base is only weakly bound to the β hydrogen in the transition state. The low Brønsted β values (Table IV), along with the value of 0.17 for *tert*-butyl chloride

TABLE IV

BRØNSTED COEFFICIENTS AND RELATIVE RATES WITH SULFUR AND OXYGEN BASES IN ELIMINATIONS FROM 2-CHLORO-2-METHYLBUTANE

Solvent	Temp, °C	β[a]	$k_{n\text{-BuS}^-}/k_{RO^-}$	$k_{PhS^-}/k_{p\text{-}MeC_6H_4}$
EtOH	55.2	0.19	5	5
i-PrOH	55.2	0.16		
t-BuOH	55.2	0.13	21	23
t-BuOH	35.2		6[d]	
t-BuOH	35.2		10[b,d]	
t-BuOH	35.2		20[c,d]	

[a] From the slope of a least squares plot of log k (Table II) *vs.* pK_a's for the substituted thiophenols in 95% ethanol at 20°: G. Schwartzenbach and E. Rudin, *Helv. Chim. Acta.* **22**, 360 (1939). [b] For 2-bromo-2-methylbutane. [c] For 2-iodo-2-methylbutane. [d] Rates with *tert*-butoxide ion from H. C. Brown and I. Moritani, *J. Amer. Chem. Soc.*, **76**, 455 (1954), and R. L. Klimisch, Ph. D. Thesis, Purdue University, 1965.

at 45° reported by McLennan,[4] give a more quantitative expression to this insensitivity. We do not wish to make too much of the β values, for those in isopropyl and *tert*-butyl alcohols utilize pK's measured in ethanol, and recent work has cast doubt on the general validity of β as a measure of the extent of proton transfer in the transition state.[25-28] We still feel that our β values at least represent proton transfers that are substantially

(22) F. G. Bordwell, *Accounts Chem. Res.*, **5**, 374 (1972).

(23) R. A. Sneen and H. M. Robbins, *J. Amer. Chem. Soc.*, **91**, 3100 (1969).

(24) I. N. Feit, E. van Dyck, and D. Wright, unpublished results.

(25) F. G. Bordwell, W. J. Boyle, Jr., J. A. Hautala, and K. C. Yee, *J. Amer. Chem. Soc.*, **91**, 4002 (1969).

(26) F. G. Bordwell and W. J. Boyle, Jr., *J. Amer. Chem. Soc.*, **93**, 511 (1971).

(27) F. G. Bordwell and W. J. Boyle Jr., *J. Amer. Chem. Soc.*, **94**, 3907 (1972).

(28) J. R. Murdoch, *J. Amer. Chem. Soc.*, **94**, 4410 (1972).

less than half complete in the transition states, for three main reasons.

First, Marcus points out that β should be a reliable measure of the extent of proton transfer if the "intrinsic barrier" (the activation energy when the free-energy differences is zero) remains nearly constant.[29] This condition is usually fulfilled when the structural variation is in oxygen or nitrogen bases, and presumably also in sulfur bases. Second, Murdoch's strictures should not apply to our reactions, which are of high activation energy[30] and unlikely to involve kinetically significant hydrogen-bonded complexes between substrate and base. Finally, England and McLennan[5,31] report substantially larger β values for the reactions of thiophenoxides with cyclohexane derivatives (0.27–0.58) and 2,2-di(*p*-chlorophenyl)-1,1,1-trichloroethane (0.77). These figures increase just as one would expect the extent of proton transfer in the transition state to increase, strongly suggesting that the much lower values with the tertiary halides indicate a low extent of proton transfer.

Experimental Section

Thiols.—All alkyl and aryl thiols except *p*-acetylthiophenol and *m*-chlorothiophenol were commercially available and were purified by standard procedures. The properties of the purified thiols agreed satisfactorily with literature values.

***p*-Acetylthiophenol** was prepared essentially in the manner described by Riesz and Frankfurter.[32] Distillation of the product at *ca.* 100° (1 mm) gave material of mp 27–29° (lit.[33] mp 27–28.5°).

***m*-Chlorothiophenol** was prepared essentially in the manner described by Campaigne and Osborn.[34] The product had bp 75° (0.3 mm), n^{25}D 1.5835 (lit.[35] n^{25}D 1.5830).

2-Chloro-2-methylbutane was Eastman White Label grade which was washed with water, dried over magnesium sulfate, and distilled at reduced pressure. Analysis by glpc on a 15 ft × 0.25 in. column of didecyl phthalate on Chromosorb P showed only 0.3% olefin. The material had bp 85°, n^{25}D 1.4038 (lit.[11,36] bp 84.3–85°, n^{20}D 1.4036).

2-Bromo-2-methylbutane.—2-Methyl-2-butanol (100 ml) was added slowly to 150 ml of 48% hydrobromic acid with stirring. The alkyl bromide was separated from the aqueous layer, washed with 5% sodium carbonate and water, and dried over magnesium sulfate. Analysis by glpc, using the same procedures as with 2-chloro-2-methylbutane, showed no detectable olefin. The material had n^{20}D 1.4425 (lit.[37] n^{20}D 1.4421).

2-Iodo-2-methylbutane.—To 50 ml of 2-methyl-2-butanol was added dropwise with stirring (magnetic stirrer) 250 g of 48% hydriodic acid. After two layers developed, the top layer was separated, washed with 5% sodium carbonate and water, and dried over magnesium sulfate. Final purification was by bulb-to-bulb distillation under reduced pressure, and the unstable product was used immediately. Analysis by glpc, using the same procedure as with 2-chloro-2-methylbutane, showed no detectable olefin. The material had n^{20}D 1.4940 (lit.[32] n^{20}D 1.4946).

Solvents.—Ethanol was distilled twice under dry nitrogen from magnesium following Lund and Bjerrum.[38] Isopropyl and *tert*-butyl alcohols were distilled twice from calcium hydride.[39]

Kinetic Procedures.—Sufficient aryl or alkyl thiol was weighed into a nitrogen-flushed 100-ml volumetric flask to provide, when filled to the mark with a standardized solution of potassium alkoxide in the corresponding alcohol, a *ca.* 0.2 *M* solution of thiolate containing 10% of unreacted thiol. The solution was brought to temperature, transferred to the reaction vessel equipped with a rubber septum for withdrawal of aliquots, and equilibrated again. Then 1.0 ml (*ca.* 0.87 g) of 2-chloro-2-methylbutane (to give a *ca.* 0.08 *M* solution) was injected from a calibrated 1.0-ml syringe and the solution was mixed rapidly. Aliquots (5 ml) were withdrawn with a calibrated syringe, quenched in cold absolute ethanol, and titrated with standardized hydrochloric acid in ethanol to a bromcresol green end point.[5] Rate constants were calculated from the usual equation for second-order reactions with unequal initial concentrations.

When the base used was selenophenoxide, the procedure was the same except that titration was to a methyl orange end point. When the base was *p*-acetyl- or *m*-chlorothiophenoxide, sharper end points resulted when the reaction was quenched in ethanol containing excess standard acid and back-titrated to the bromcresol green end point with standard ethoxide in ethanol. As a control, these two variants on the usual technique were tried with thiophenoxide. All three techniques gave rate constants within experimental error of each other. The hydrochloric acid in ethanol was standardized weekly with sodium carbonate to a methyl orange end point in water. The ethoxide in ethanol used for back-titration was standardized with potassium acid phthalate to a phenolphthalein end point in water.

The solvolysis reactions of the tertiary halides in ethanol and 2-propanol were measured over the first 20–30% of reaction by quenching the aliquots in cold absolute ethanol and titration to the bromcresol green end point with ethoxide in ethanol.

Observed rate constants are recorded in Table I.

Corrected Rate Constants and Brønsted Coefficients.—The observed rate constants were corrected for solvolysis following McLennan.[5] No other correction was made for nonquantitative olefin formation, as all of the 5–10% of substitution product arises from the first-order reaction. The corrected rate constants are given in Table II. Brønsted coefficients were calculated from these corrected rate constants by the method of least squares, using the pK_a values of the thiophenols in 95% ethanol reported by Schwartzenbach and Rudin.[40] These form the most complete series available. No pK_a's in the higher alcohols are available.

Olefin Proportions.—Solutions of the thiolate with 10% excess thiol were prepared and standardized as in the kinetic runs. The appropriate amount of alkyl halide was weighed into a 10-ml volumetric flask and the flask was filled to the mark with the thiolate solution. The contents was transferred immediately to a stainless-steel reaction tube with a gas-tight seal[41] and the reaction was allowed to run to completion. The reaction mixture was then analyzed directly on an Aerograph A-90-P2 gas chromatograph with thermal conductivity detector, using either a 20 ft × 0.25 in. column of 20% adiponitrile on Chromosorb P-AW, 60–80 mesh, or a 15 ft × 0.25 in. column of 20% didecyl phthalate on Chromosorb P, both columns being operated at 30°. Usual concentrations were alkyl halide, 0.08 *M*, and base, 0.2, 0.5, or 1.0 *M*. Results are recorded in Table III.

Acknowledgment.—We thank Professor I. N. Feit for information in advance of publication on his investigations of E1 reactions.

Registry No.—C_6H_5OK, 100-67-4; 2-chloro-2-methylbutane, 594-36-5; 2-bromo-2-methylbutane, 507-36-8; 2-iodo-2-methylbutane, 594-38-7.

(29) R. A. Marcus, *J. Amer. Chem. Soc.*, **91**, 7224 (1969).

(30) Our limited temperature-dependence data do not permit the calculation of precise activation energies, but figures in the range of 16–23 kcal/mol can be estimated.

(31) B. D. England and D. J. McLennan, *J. Chem. Soc. B*, 696 (1966).

(32) E. Riesz and W. Frankfurter, *Monatsh. Chem.*, **50**, 72 (1928).

(33) A. H. Herz and D. S. Tarbell, *J. Amer. Chem. Soc.*, **75**, 4657 (1953).

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(37) H. C. Brown and H. Stern, *J. Amer. Chem. Soc.*, **72**, 5068 (1950).

(38) H. Lund and J. Bjerrum, *Chem. Ber.*, **64**, 210 (1931).

(39) H. C. Brown and R. L. Klimisch, *J. Amer. Chem. Soc.*, **88**, 1425 (1966).

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(41) W. H. Saunders, Jr., and T. A. Ashe, *J. Amer. Chem. Soc.*, **91**, 4473 (1969).

Alkaline Hydrolysis of Methylthiopurines Bearing Oxo Groups in the Ring

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Received February 26, 1973

The susceptibility of methylthiopurines, bearing also oxo groups, to alkaline hydrolysis was studied. Those derivatives which lack *N*-methyl substituents are refractory. The *N*-monomethyl derivatives of the series react as anions; attack is directed exclusively toward methylthio groups, placed in the same ring as the *N*-methyl substituent. *N*,*N*′-Dimethyl compounds undergo alkaline hydrolysis as neutral molecules. Here hydrolysis of a methylthio group in the pyrimidine ring is preferred over attack on a methylthio substituent in the imidazole moiety. In all cases, polarization of *N*-methyl groups creates a positive center which directs the attack by hydroxyl ion.

We have shown recently that methylthiopurines, which are able to form anions, are not hydrolyzed by alkali. On the other hand, *N*-methyl derivatives of methylthiopurines, which lack an ionizable NH group, are susceptible to nucleophilic attack, the direction of the reaction being determined by the position of the *N*-methyl substituent.[1]

The present study is concerned with the hydrolysis of methylthiopurines, bearing also an oxo group. The substrates used comprise mono-NMe derivatives, which still have a free NH group and therefore react with alkali as anions, and bis-*N*-methylpurines, which lack NH groups and thus are attacked as neutral molecules. We shall show that, here again, the position of the *N*-methyl substituent determines the feasibility and the course of the hydrolysis.

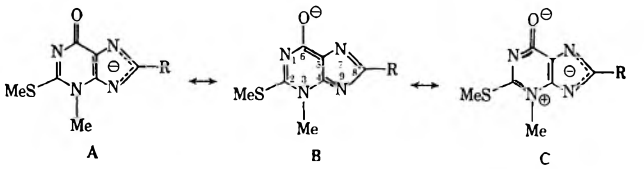
Attack of Hydroxyl Ion on Anionic Substrates.— All methylthiooxopurines, lacking *N*-methyl substituents, are resistant to weak (pH ~9) or strong bases (2 *N* NaOH), *i.e.*, neither the mono- nor the dianions are attacked. *E.g.*, 2,8-dimethylthiohypoxanthine shows p*K* values of 7.5 and 10.75. At pH 9, mainly the monoanion, formed by dissociation of the 1-NH group,[2] is present in aqueous solution. Although in this anion the negative charge is confined to the pyrimidine ring, the 8-SMe substituent is not replaced by OH^-.

The derivatives, bearing a single *N*-methyl group, can be divided into two classes. In class a, the *N*-methyl group facilitates hydrolysis of a neighboring *S*-methyl substituent (compounds 2, 6, 7, and 12, Table I). This effect is observed even if the second neighbor is a carbonyl group (as in 1, 5, and 8). In class b, on the contrary, an *N*-methyl group in one moiety of the purine ring, whether adjacent to a C=N— double bond (3, 4) or to a carbonyl group (10, 13, 20, 21, 22, and 23), does not support hydrolysis of an S–Me substituent in the second moiety.

Table I also includes the p*K* values for anion formation in the substrates studied. It is evident that, at pH 14, both reactive and refractory purines are completely ionized. Therefore the presence of a negative charge as such is not sufficient to explain the resistance of certain derivatives to alkaline hydrolysis. However, the location of the NH groups, undergoing dissociation, relative to the methylthio substituents is of great importance.

The facilitatory influence of an *N*-methyl group is ascribed to its polar form. This is shown in Scheme I

SCHEME I

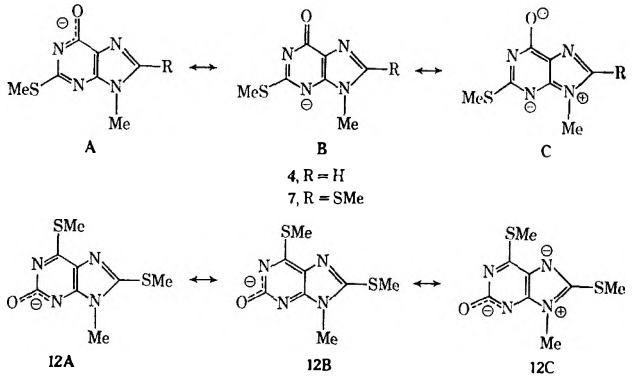


2, R = H
6, R = SMe

for the anions 2 and 6, A–C. In the mesomeric form **C**, the pyrimidine ring possesses an aromatic structure; here, the positive charge at N-3 directs attack of OH^- to the 2–3 bond. In 6, the 8-methylthio group is resistant to alkaline hydrolysis.

The counterpart to these two cases is represented by 7 and 12. Here the negative charge of the anion is confined to the pyrimidine ring (Scheme II). Attack of

SCHEME II



4, R = H
7, R = SMe

OH^- at position 8 is facilitated in the polar form **7C**. The analogous interpretation is assumed for the anion of 12 (Scheme II).

For the derivatives 1, 5, and 8, in which the 1-methyl substituent is located between an SMe and a carbonyl group, Scheme III demonstrates that the "aromatic" resonance forms 1C, 5C, and 8C facilitate attack at the carbon atom in the pyrimidine ring, bearing an SMe group. Again in 5, the 8-methylthio substituent is refractory to alkaline hydrolysis.

By a similar way of reasoning, we may explain the resistance to hydrolysis of the members of class b. In the anions of 3 and 4, the positive charge is confined to the imidazole ring; thus reaction at position 2 is not possible (see the polar forms of 4 in Scheme II). In the anion of 10, structure C is assumed to make the greatest contribution (Scheme III). Here the imidazole ring is

(1) U. Reichman, F. Bergmann, D. Lichtenberg, and Z. Neiman, *J. Org. Chem.*, **38**, 2066 (1973).

(2) U. Reichman, F. Bergmann, and D. Lichtenberg, *J. Chem. Soc., Perkin Trans. 1*, in press.

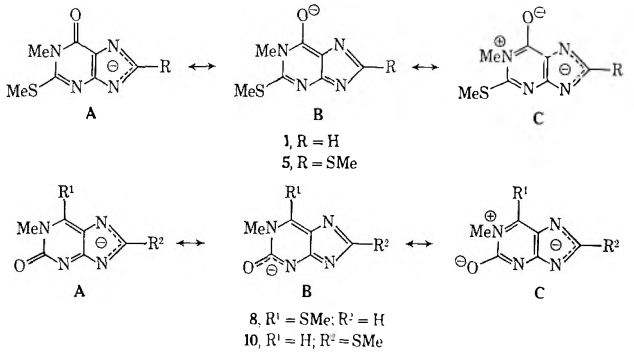
TABLE I

HYDROLYSIS OF METHYLTHIO GROUPS IN THE ANIONS OF OXOPURINES

No.	Compd	p*K* for anion formation	Position attacked[a]	Product formed
		A. Hypoxanthines		
1	1-Methyl-2-methylthio-	9.5	2	1-Methylxanthine (18)
2	3-Methyl-2-methylthio-	8.7	2	3-Methylxanthine (19)
3	7-Methyl-2-methylthio-	8.0		
4	9-Methyl-2-methylthio-	9.5		
5	1-Methyl-2,8-dimethylthio-	8.2	2	1-Methyl-8-methylthioxanthine (20)
6	3-Methyl-2,8-dimethylthio-	7.9	2	3-Methyl-8-methylthioxanthine (21)
7	9-Methyl-2,8-dimethylthio-	7.5	8	9-Methyl-2-methylthio-6,8-dioxopurine (22)
		B. 2-Oxopurines		
8	1-Methyl-6-methylthio-	8.8	6	1-Methylxanthine (18)
9	3-Methyl-6-methylthio-	7.7	6	3-Methylxanthine (19)
10	1-Methyl-8-methylthio-	7.1		
11	3-Methyl-6,8-dimethylthio-	6.6	6	3-Methyl-8-methylthioxanthine (21)
12	9-Methyl-6,8-dimethylthio-	6.2	8	9-Methyl-6-methylthio-2,8-dioxopurine (23)
		C. 8-Oxopurines		
13	9-Methyl-2,6-dimethylthio-	8.8		

[a] All compounds were hydrolyzed by method A, with the exception of 3, 4, 10, and 13 which were recovered unchanged after use of method C.

SCHEME III

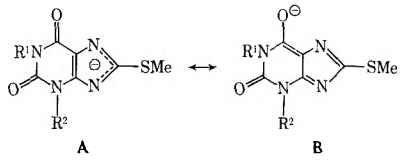


1, R = H
5, R = SMe

8, R¹ = SMe; R² = H
10, R¹ = H; R² = SMe

protected by its negative charge against nucleophilic attack at position 8. This applies also to **20** and **21** (Scheme IV).

SCHEME IV

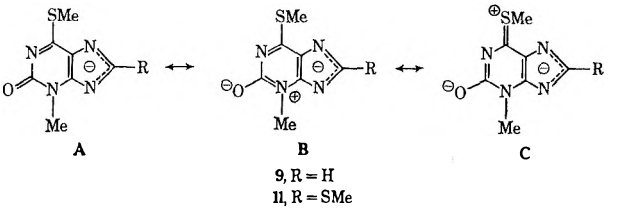


20, R¹ = H; R² = Me
21, R¹ = Me; R² = H

In the 3-methyl-2-oxo derivatives **9** and **11**, the *N*-methyl substituent facilitates hydrolysis of the remote 6-SMe group. Here the anion can be represented by the polar structures **A**–**C** (Scheme V). It appears that the 6-SMe group can acquire a formal positive charge *via* the polar form **C**, which facilitates attack by OH^- at the 1–6 bond. It is also evident that the 8-SMe group in **11** is protected by the negative charge of the imidazole ring.

Attack of Hydroxyl Ion on Uncharged Substrates. — The oxo derivatives in Table II bear two *N*-methyl substituents and thus are unable to form anions. In the members of this group, hydrolysis in the pyrimidine ring is preferred over attack at the 8-SMe group. Scheme VI shows the mesomeric forms of

SCHEME V



9, R = H
11, R = SMe

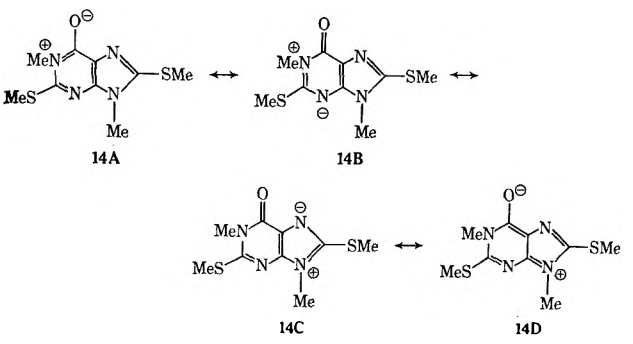
TABLE II

ALKALINE HYDROLYSIS OF METHYLTHIO GROUPS IN NEUTRAL MOLECULES OF OXOPURINES

No.	Compd	Position[a] attacked	Product formed
14	1,9-Dimethyl-2,8-dimethylthiohypoxanthine	2	1,9-Dimethyl-8-methylthioxanthine (24)
15	3,7-Dimethyl-6-methylthio-2-oxopurine	6	Theobromine (25)
16	3,7-Dimethyl-2,8-dimethylthiohypoxanthine	2	3,7-Dimethyl-8-methylthioxanthine (26)
17	3,7-Dimethyl-6,8-dimethylthio-2-oxopurine	6	26

[a] All purines in Table II were hydrolyzed by method B.

SCHEME VI

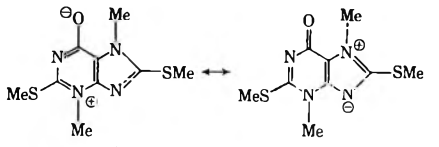


the 1,9-dimethyl derivative **14**. In the polar structures **A** and **B**, the positive charge at N-1 is close to the 2-SMe group. Form **A** is assumed to make the greatest contribution, in view of the aromatic struc-

ture of its pyrimidine ring. In order to explain the preference of position 2 over 8 for attack by OH^-, we may assume that forms **14C** and **D** are less important than **14A**, presumably because of the lack of aromatic structure.

In analogy, we describe 3,7-dimethyl-2,8-dimethylthiohypoxanthine (**16**) by the resonance forms **A–B** in Scheme VII. In **16A**, the pyrimidine ring exhibits aromatic character; this may be responsible for attack at C-2 rather than at C-8 to give 1,9-dimethyl-8-methylthioxanthine (**24**).

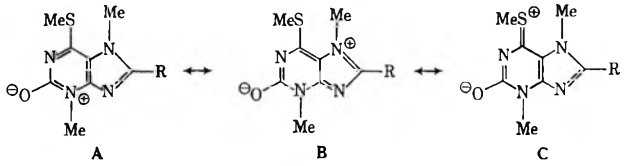
SCHEME VII



16A 16B

The two 3,7-dimethyl-2-oxo derivatives **15** and **17** are attacked at position 6. This shows that among the three mesomers **A–C** (Scheme VIII), form **C** in which a positive charge is placed at the 6-SMe group, similar to **11C**, is responsible for directing nucleophilic attack towards position 6. However, it is difficult to see why in mesomer **17B** reaction at position 8 should not be facilitated. Careful analysis of the reaction mixture revealed only the presence of 3,7-dimethyl-8-methylthioxanthine (**26**), no traces of the isomeric 3,7-dimethyl-6-methylthio-2,8-dioxopurine being detected.

SCHEME VIII



A B C

15, R = H
17, R = SMe

We have sought an explanation for the predominant participation of **14A** and **17C** by theoretical considerations. Following Fukui's method,[3] we have determined the sequence of susceptibility to nucleophilic attack for purines **14**, **16**, and **17** (Table III). For the first two compounds, calculation of superdelocalizabilities for nucleophilic attack shows preference of C-2 over C-8, in agreement with our experimental results. However, for **17** we calculate the sequence 8 → 6, while the reverse has been found experimentally (Table II).

TABLE III

SUPERDELOCALIZABILITIES FOR NUCLEOPHILIC ATTACK

No.	Compd	Superdelocalizability of position 2	6	8	Sequence
14	1,9-Dimethyl-2,8-dimethylthiohypoxanthine	0.874		0.766	2 > 8
16	3,7-Dimethyl-2,8-dimethylthiohypoxanthine	0.894		0.827	2 > 8
17	3,7-Dimethyl-6,8-dimethylthio-2-oxopurine		0.819	0.847	8 > 6

A tentative explanation for this discrepancy may be based on Scheme VIII by assuming that attack of OH^- between 6-SMe and 7-NMe in **17B** or **C** is less obstructed than approach of OH^- to the $C^8{=}N^7$ double bond in **17B**. This is suggested by FMM models[4] which show that rotation of the 6-SMe group is less hindered by the 7-alkyl substituent than is that of the 8-SMe group in **17**. Considerations of steric hindrance do not enter into Fukui's calculations.

Evidence for the Structure of the Dioxo Products, Obtained by Alkaline Hydrolysis.—The xanthines **18**,[5] **19**, and **25** were identified by comparison with authentic samples (uv and nmr spectra; R_F values). Compounds **20**, **21**, and **24** were synthesized independently from the corresponding *N*-methyl-8-thiouric acids.[6,7] Among the latter, the 1-methyl derivative **28** is new (see Experimental Section). In addition, the structure of 3-methyl-8-methylthioxanthine **21** follows from the fact that the same product results from hydrolysis of either **6** or **11** (see Table I). Likewise, **26** is obtained by hydrolysis of either **16** or **17** (Table II).

22 differed in all its properties from the alternative product that would result from attack at position 2, *viz.* 9-methyl-8-methylthioxanthine **27**, which was prepared by an independent route (Table IV). In **22**, the 9-methyl substituent is adjacent to an 8-oxo group. The $\delta_{9\text{-Me}}$ value (3.47 ppm) is shifted upfield by 0.39 ppm, relative to the corresponding signal in **27** ($\delta_{9\text{-Me}}$ 3.86).

Compound **23** proved identical with an authentic sample, obtained by S-methylation of the new 9-methyl-6-thiouric acid **29** (see Experimental Section).

Experimental Section

All melting points are uncorrected; analyses were performed by F. Strauss, Oxford, England. For chromatography on Whatman No. 1 paper by the descending method, the following solvents were used: solvent A, 1-butanol–acetic acid–water (12:3:5, v/v); solvent B, ethanol–DMF–water (3:1:1, v/v). Spots were detected by their fluorescence under a Mineralight uv lamp (λ ~254 nm). Uv spectra were measured on a Hitachi Perkin-Elmer Model 124 spectrophotometer and nmr spectra on a Jeol MH-100 instrument, using TSP (sodium 3-trimethylsilylpropionate-*2,2,3,3-d*$_4$ of Merck Sharp and Dohme, Canada), as internal standard. p*K* values were determined by the spectrophotometric method, plotting λ_{max} as function of pH.

I. Alkaline Hydrolysis. General Procedures.—In all experiments, 1 mmol of substrate and 10 ml of 2 *N* NaOH were used. The pH during and after the reaction was above 14.

Method A.—A solution of the substrate in 2 *N* NaOH was refluxed for 3 hr. The pH was brought to 6 by addition of glacial acetic acid. The precipitate was filtered, washed with cold water, and purified as described in Table IV.

Method B.—A suspension of the substrate in 2 *N* NaOH was stirred and refluxed for 5 min. The clear solution was rapidly cooled and acidified.

Method C.—A suspension of the substrate in 2 *N* NaOH was stirred and refluxed until a clear solution was obtained, but in any case not less than 5 hr. Acidification and further treatment followed method A.

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(4) Framework Molecular Models, Nutley, N. J.

(5) G. B. Elion, *J. Org. Chem.*, **27**, 2478 (1962).

(6) F. Bergmann, H. Kwietny-Govrin, H. Ungar-Waron, A. Kalmus, and M. Tamari, *Biochem. J.*, **86**, 567 (1963).

(7) H. Biltz, K. Strufe, E. Topp, M. Heyn, and R. Roll, *Justus Liebigs Ann. Chem.*, **423**, 200 (1921).

TABLE IV

PHYSICAL PROPERTIES OF NEW OXOPURINES

Compd	λ_{max}, nm,[a] at pH 1	λ_{max}, nm,[a] at pH 6	λ_{max}, nm,[a] at pH 12	Mp, °C	Method of preparation[b]	Solvent for crystallization	Crystal form and color	R_f in solvent[c] A	R_f in solvent[c] B	Fluorescence[d]
I. *N*-Methylthiouric Acids										
28[e] 1-Methyl-8-thiouric acid	243 (4.07) 295 (4.42)	253 (4.30)[f] 299 (4.30)		>300	See Experimental Section	NH_3–acetic acid	Yellow microcrystals	0.41	0.62	Greenish
29[e] 9-Methyl-6-thiouric acid	259 (3.84) 356 (4.18)	349 (4.43)[f]		>300	See Experimental Section	NH_3–acetic acid	Yellow microcrystals	0.38	0.57	Greenish
II. Derivatives of 2,8-Dimethylthiohypoxanthine										
6[e] 3-Methyl-	297.5 (4.30)	297.5 (4.30)	303 (4.30)	298–299	II[g]	1-Butanol	Colorless plates	0.79	0.55	Bright violet
14[e] 1,9-Dimethyl-	283 (4.42)	279 (4.32)		210–212	See Experimental Section	Ethyl acetate	Colorless needles	0.89	0.74	Dark violet
16[e] 3,7-Dimethyl-	297.5 (4.30)	297.5 (4.30)		190	From **6** (see Experimental Section)	Ethyl acetate	Colorless needles	1.0	0.9	Blue
III. Derivatives of 8-Methylthioxanthine										
20[e] 1-Methyl-	289 (4.17)	293 (4.14)	295 (4.16)	>300	II (from **28**); hydrolysis of **5**	Ethanol	Colorless plates	0.87	0.74	Dark violet
21[e] 3-Methyl-	291 (4.25)	295 (4.15)	294 (4.43)	>300	II; hydrolysis of **6** and **11**	Ethanol	Colorless rods	0.87	0.74	Dark violet
27[e] 9-Methyl-	285	287	291	>300	II[h]	Dil acetic acid	Colorless plates	0.90	0.79	Dark violet
24[e] 1,9-Dimethyl-	285 (4.20)	287 (4.20)	291 (4.17)	>300	See Experimental Section; hydrolysis of **14**	1-Butanol	Colorless boats	0.83	0.71	Dark violet
26[e] 3,7-Dimethyl-	294 (4.23)	295 (4.23)	295 (4.12)	268	Hydrolysis of **16** and **17**	Ethanol	Colorless needles	0.86	0.75	Dark violet
IV. Other 9-Methyl Derivatives										
22[e] 2-Methylthio-6,8-dioxopurine	278 (4.12)	281 (4.14)	287 (4.14)	>300	Hydrolysis of **7**	1-Butanol	Colorless microcrystals	0.83	0.70	Dark violet
23[e] 6-Methylthio-2,8-dioxopurine	341 (4.20)	335 (4.20)	329 (4.23)	>300	II (from **29**); hydrolysis of **12**	Ethanol	Colorless microcrystals	0.75	0.69	Blue

[a] Figures in brackets designate log ϵ_{max}. [b] Methods of preparation; see Experimental Section. All compounds prepared by methylation according to method II were obtained in nearly quantitative yield. [c] For solvents A and B, see Experimental Section. [d] Under a Mineralight uv lamp (λ ~254 nm). [e] Satisfactory combustion analytical data for C, H, N, S were reported for these compounds: Ed. [f] At pH 8.0. [g] From 3-methyl-2,8-dithiouric acid [U. Reichman, F. Bergmann, D. Lichtenberg, and Z. Neiman, *J. Chem. Soc., Perkin Trans. 1*, 793 (1973)]. [h] By methylation of 9-methyl-8-thiouric acid.[7]

II. S-Methylation.—Solutions of the thio compounds in 2 *N* NaOH were stirred at room temperature with 2 equiv of methyl iodide. The precipitate, obtained after acidification, was purified as shown in Table IV.

The following compounds were synthesized by known procedures: **3**, **4**, **5**, **7**, **9**, **10**, **11**, **12**, and **13**;[1] **1**;[5] **2** and **8**;[8] 3-methyl-8-thiouric acid;[6] 9-methyl- and 1,9-dimethyl-8-thiouric acid;[7] 3,7-dimethyl-6-methylthio-2-oxopurine (**15**);[9] 1- (**18**)[5] and 3-methylxanthine (**19**).[10] Synthesis of 3,7-dimethyl-6,8-dimethylthio-2-oxopurine (**17**) will be published elsewhere.

New Purines. 3,7-Dimethyl-2,8-dimethylthiohypoxanthine (16).—A solution of 3-methyl-2,8-dimethylthiohypoxanthine (**6**) (0.5 g) in acetonitrile (400 ml) and methyl iodide (2 ml) was refluxed for 4 hr. The solvent was removed *in vacuo* and the residue shaken with cold 2 *N* NaOH. The insoluble portion crystallized from ethyl acetate, mp 190° (see Table IV).

1-Methyl-8-thiouric Acid (29).—A solution of 1-methyl-4,5-diaminouracil[11] (2 g) in dry pyridine (150 ml) and carbon disulfide (10 ml) was refluxed for 5 hr. The solvent was removed *in vacuo*, the residue dissolved in ammonia (charcoal), and the solution filtered and acidified, mp >300° (see Table IV).

9-Methyl-6-thiouric Acid (28).—A mixture of 4,5-diamino-6-thiouracil[12] (4 g) and methyl isocyanate (2.5 g) in pyridine (100 ml) was stirred and refluxed for 3 hr. The solvent was distilled *in vacuo* and the residue stirred with acetone. The insoluble portion was stirred and heated during 5 hr with concentrated HCl (100 ml). The product was dissolved in concentrated ammonia (charcoal) and reprecipitated with glacial acetic acid, mp >300°.

1,9-Dimethyl-2,8-dimethylthiohypoxanthine (14).—A solution of 1-methyl-2,8-dimethylthio-6-thiopurine[1] (1 g) in 2 *N* NaOH (7.5 ml) was stirred at room temperature with methyl iodide (2 ml) for 15 min. The precipitate formed was filtered; yield of **14**, 60%.

From the filtrate, the second product (**5**) separated after addition of glacial acetic acid.

Calculation of Superdelocalizabilities for 14, 16, and 17.—π-Electronic Hückel-type calculations were performed with the use of Pullman's[13] parametrization, to construct the Hückel topological matrices. After diagonalization (Jacobi's method), the coefficients of the wave functions were subjected to a "frontier" analysis according to Fukui.[3] All computations were performed on a CDC 6400 digital computing machine using a Fortran program.

(8) Z. Neiman and F. Bergmann, *Israel J. Chem.*, **3**, 85 (1965).
(9) K. R. H. Wooldridge and R. Slack, *J. Chem. Soc.*, 1863 (1962).
(10) H. Bredereck, H. G. von Schuh, and A. Martin, *Chem. Ber.*, **83**, 201 (1950).
(11) W. Pfleiderer, *Chem. Ber.*, **90**, 2272 (1957).
(12) G. Levin, A. Kalmus, and F. Bergmann, *J. Org. Chem.*, **25**, 1752 (1960).
(13) A. Pullman and B. Pullman, "Quantum Biochemistry," Interscience, New York, N. Y., 1963, p 108.

Acknowledgment.—This research was supported in part by a grant (to U. R.) of the California Foundation for Biochemical Research.

Registry No.—1, 33867-98-0; 2, 40959-21-5; 5, 39013-76-8; 6, 40959-22-6; 7, 39062-23-2; 8, 38759-23-8; 9, 38759-24-9; 11, 39013-78-0; 12, 40848-20-2; 14, 40848-21-3; 15, 38759-27-2; 16, 40848-23-5; 17, 40848-24-6; 20, 34617-98-6; 21, 40848-26-8; 22, 40848-27-9; 23, 40848-28-0; 24, 40848-29-1; 26, 40959-23-7; 27, 40848-30-4; 28, 40848-31-5; 29, 40848-32-6; 1-methyl-4,5-diaminouracil, 40959-24-8; 4,5-diamino-6-thiouracil, 40848-33-7; carbon disulfide, 75-15-0; acetone, 67-64-1; 1-methyl-2,8-dimethylthio-6-thiopurine, 39008-25-8.

Hydrolysis of 2,4-Dinitrophenyl Sulfate in Benzene in the Presence of Alkylammonium Carboxylate Surfactants

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Received June 14, 1973

Alkylammonium carboxylates markedly enhance the hydrolysis of 2,4-dinitrophenyl sulfate in benzene. The observed rate constants increase sigmoidally with increasing surfactant concentration in the region of the critical micelle concentration and linearly at higher surfactant concentrations. Rate constants are analyzed in terms of micellar and composite general-acid and general-base catalysis. The micellar catalyzed rates in benzene in the presence of alkylammonium carboxylates are factors of 21- to 70-fold greater than that obtained for the hydrolysis of 2,4-dinitrophenyl sulfate in water. The observed micellar catalysis is discussed in terms of solubilization of 2,4-dinitrophenyl sulfate in the polar micellar cavity where it is held fairly rigidly (as indicated by the remarkably large decrease in the entropy of activation with respect to that in water) and enhanced water activity and proton transfer assist the rate-determining S–O bond fission. Linear dependencies have been observed between the logarithms of rate constants for micellar and combined general-acid and -base catalysis and the number of carbon atoms in both the carboxyl and ammonium groups of the alkylammonium carboxylates. Changes in the chain length of the carboxyl and ammonium groups affect the micellar catalysis to the same extent, but general-acid catalysis depends on the chain length to a greater extent than general-base catalysis.

Rate constants for the mutarotation of 2,3,4,6-tetramethyl-α-D-glucose,[1] for the decomposition of σ complexes,[2] for the aquation of chromium(III) and cobalt(III) complexes,[3] and for the trans–cis isomerization of bis(oxalato)diaquochromate(III) anion[4] are enhanced remarkably by alkylammonium carboxylate surfactants in nonpolar solvents. These rate enhancements have been rationalized in terms of favorable substrate partitioning in the polar cavities of reversed micelles, dynamically formed from alkylammonium carboxylates,[5–8] where specific interactions, proton transfer, and enhanced water activity provide the driving force for the catalysis. Rate constants for these reactions in the reversed micellar environment in nonpolar solvents are orders of magnitude greater than those in the pure nonpolar solvents and in water.[1–5] Simple partitioning by itself is clearly an inadequate explanation for rate enhancements of this magnitude. It is likely that substrates are being held more rigidly in the polar cavities of reversed micelles than they are in aqueous "normal" micelles. This factor and the presence of a polar interior render, we believe, reversed micelles not only an inherently unique reaction media but a potentially fruitful model for biomembranes and enzymatic interactions.

Investigations of aquation and isomerization of chromium(III) complexes[3,4] indicated that, other factors being the same, alkylammonium carboxylate micelles enhance the rates of acid-catalyzed reactions to the greatest extent when the neutral rate is relatively small. In order to probe this contention further and to extent the range of reversed micellar interactions to hydrolyses, we have examined the hydrolysis of 2,4-dinitrophenyl sulfate in benzene in the presence of micelle-forming alkylammonium carboxylates. Our selection was somewhat governed by the availability of information on the mechanisms of 2,4-dinitrophenyl sulfate hydrolyses in water[9,10] and in aqueous micellar solutions in the absence[11] and presence[12] of nucleophilic reagents. Additionally, ^{1}H nmr investigations indicated that in aqueous zwitterionic 3-(dimethyldodecylammonio)propane-1-sulfonate micelles the environment of 2,4-dinitrophenyl sulfate is somewhat hydrophobic but its *in situ* hydrolysis products interact to a greater extent with the polar head groups of the micelle than the substrate.[13]

Experimental Section

The preparation and purification of 2,4-dinitrophenyl sulfate has been described.[10]

Reagent-grade benzene (<0.02% water) was distilled from

(1) E. J. Fendler, J. H. Fendler, R. T. Medary, and V. A. Woods, *Chem. Commun.*, 1497 (1971); J. H. Fendler, E. J. Fendler, R. T. Medary, and V. A. Woods, *J. Amer. Chem. Soc.*, **94**, 7288 (1972).

(2) J. H. Fendler, *J. Chem. Soc., Chem. Commun.*, 269 (1972); J. H. Fendler, E. J. Fendler, and S. A. Chang, *J. Amer. Chem. Soc.*, **95**, 3273 (1973).

(3) C. J. O'Connor, E. J. Fendler, and J. H. Fendler, *J. Amer. Chem. Soc.*, **95**, 600 (1973); C. J. O'Connor, E. J. Fendler, and J. H. Fendler, unpublished work.

(4) C. J. O'Connor, E. J. Fendler, and J. H. Fendler, unpublished work.

(5) E. J. Fendler, S. A. Chang, J. H. Fendler, R. T. Medary, O. A. El Seoud, and V. A. Woods in "Reaction Kinetics in Micelles," E. H. Cordes, Ed., Plenum Press, New York, N. Y., 1973, p 127.

(6) J. H. Fendler, E. J. Fendler, R. T. Medary, and O. A. El Seoud, *J. Chem. Soc., Faraday Trans. 1*, **69**, 280 (1973).

(7) E. J. Fendler, J. H. Fendler, R. T. Medary, and O. A. El Seoud, *J. Phys. Chem.*, **77**, 1432 (1973).

(8) O. A. El Seoud, E. J. Fendler, J. H. Fendler, and R. T. Medary, *J. Phys. Chem.*, **77**, 1876 (1973).

(9) S. J. Benkovic and P. A. Benkovic, *J. Amer. Chem. Soc.*, **88**, 5504 (1966).

(10) E. J. Fendler and J. H. Fendler, *J. Org. Chem.*, **33**, 3852 (1968).

(11) E. J. Fendler, R. R. Liechti, and J. H. Fendler, *J. Org. Chem.*, **35**, 1658 (1970).

(12) J. H. Fendler, E. J. Fendler, and L. W. Smith, *J. Chem. Soc., Perkin Trans. 2*, 2097 (1972).

(13) E. J. Fendler, C. L. Day, and J. H. Fendler, *J. Phys. Chem.*, **76**, 1460 (1972).

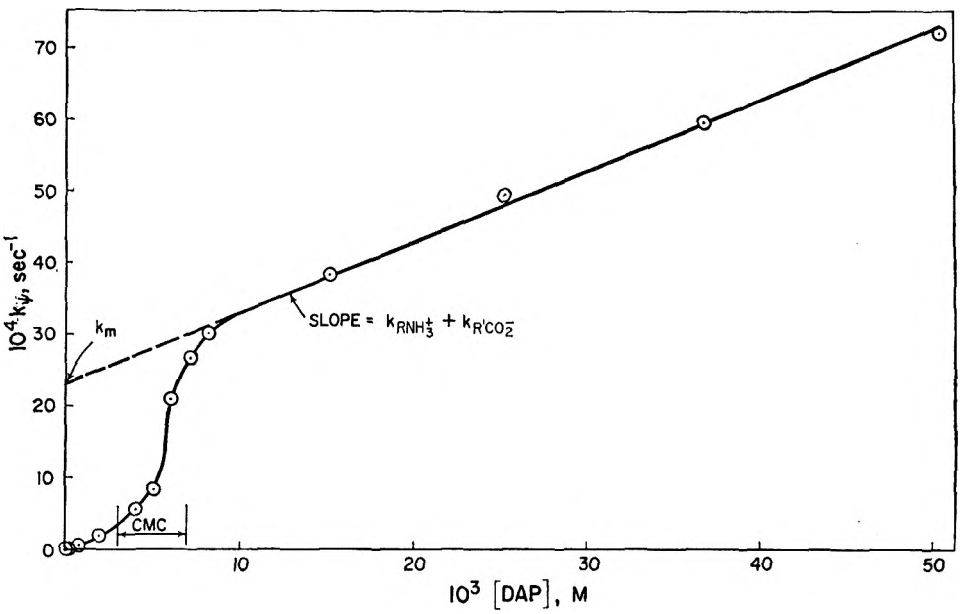

Figure 1.—Observed rate constants for the hydrolysis of 2,4-dinitrophenyl sulfate as a function of the concentration of dodecylammonium propionate in benzene at 39.8°.

sodium onto freshly activated Linde Type 5A Molecular Sieve and stored under nitrogen.

Octylammonium propionate (OAP), butyrate (OAB), nonanoate (OAN), dodecanoate (OAD), and tetradecanoate (OAT), butyl (BAP), hexyl (HAP), decyl (DeAP), and dodecyl ammonium propionate (DAP), dodecylammonium butyrate (DAB), and dodecylammonium benzoate (DABz) were prepared by the method of Kitahara[14] as described previously.[6-8] The purity of these surfactants was established by the observation of sharp melting or boiling points and by their infrared and proton magnetic resonance spectra.[6-8] Surfactants were dried on a high vacuum line for at least 12 hr immediately prior to making up the stock solutions in benzene. Some of these surfactants are very hygroscopic and appropriate care was taken to exclude atmospheric moisture in making up the stock solutions.

Rates of hydrolysis were measured spectrophotometrically by determining the absorbances of the liberated phenol at 347 nm as a function of time on a Beckman Kintrac VII recording spectrophotometer. The temperature of the thermostated bath and the cell compartment was maintained within ±0.05°, as monitored by NBS thermometers. Good first-order plots were obtained in all cases for at least 75% reaction. Pseudo-first-order rate constants, k_ψ, have been calculated by the Guggenheim method.[15] Reactions were initiated by adding *ca.* 1 mg of solid 2,4-dinitrophenyl sulfate to 5 ml of the reaction solution which had been preequilibrated at the appropriate temperature. After vigorous shaking for several seconds the mixture was filtered directly into a cell and placed in the thermostated cell compartment of the spectrophotometer. The overall concentration of 2,4-dinitrophenyl sulfate in the reaction mixture was 1–6 × 10^{-5} *M*. Spectrophotometric analysis established 2,4-dinitrophenol as the sole reaction product.[12]

Results and Discussion

2,4-Dinitrophenyl sulfate hydrolyzes in benzene in the presence of alkylammonium carboxylate surfactants. Lack of substrate solubility prevented the examination of its hydrolysis rate in pure benzene, but it is expected to be negligible. The most detailed investigation utilized dodecylammonium propionate (DAP). At the lowest DAP concentration (1.17 × 10^{-4} *M*) the hydrolysis rate is considerably lower than that in water (Table I). Increasing concentrations of the surfactants increase the hydrolysis rate. This increase is sigmoidal

Table I
Rate Constants for Hydrolysis of 2,4-Dinitrophenyl Sulfate in Benzene in the Presence of DAP

Temp 24.5°		Temp 39.8°	
10^3 [DAP], *M*	$10^4 k_\psi$, sec^{-1}	10^3 [DAP], *M*	$10^4 k_\psi$, sec^{-1}
	0.27[a]		1.45[a]
5.06	3.99	0.117	0.045
10.1	8.82	0.468	0.166
11.7	9.94	0.701	0.237
25.3	12.9	0.935	0.402
50.6	18.5	1.01	0.427
75.9	22.4	2.02	1.83
101	28.5	4.05	5.48
142	40.5	5.06	8.28
189	45.7	6.06	21.1
202	48.2	7.08	26.7
208	49.2	8.09	30.2
237	55.0	15.2	38.3
293	66.7	25.3	49.4
402	86.9	50.6	71.4
501	104		
610	125		

[a] In water at pH 8.0 in the presence of 2.5 × 10^{-3} *M* $Na_2B_4O_7$ buffer, taken from ref 11.

in the region of the critical micelle concentration, after which it continues to increase linearly (Figure 1). Markedly different types of kinetic rate profiles have been found for micellar catalysis in aqueous solution.[16-19] However, saturation type kinetics are generally observed in which a sigmoidal rate enhancement is followed by a plateau. In some cases the plateau becomes rather short and increasing surfactant concentration decreases the observed rate (*i.e.*, a rate maximum is observed). Both of these types of kinetic behavior have been observed for reactions catalyzed by reversed micelles in nonpolar solvents.[1-5] The present data (Table I) indicate that, in addition to micellar

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(15) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).
(16) E. H. Cordes and R. B. Dunlap, *Accounts Chem. Res.*, **2**, 329 (1969).
(17) E. J. Fendler and J. H. Fendler, *Advan. Phys. Org. Chem.*, **8**, 271 (1970).
(18) T. C. Bruice in "The Enzymes," 3rd ed, Vol. 2, Academic Press, New York, N. Y., 1970, p 217.
(19) E. H. Cordes and C. Gitler, *Progr. Bioorg. Chem.*, **2**, 1 (1973).

catalysis, components of dodecylammonium propionate also enhance the hydrolysis rate. The observed rate constant for the hydrolysis of 2,4-dinitrophenyl sulfate at a given DAP concentration, or more generally at a given alkylammonium carboxylate concentration, k_ψ, can be described by eq 1, where k_m is the rate constant

$$k_\psi = k_m + (k_{RNH_3^+} + k_{-O_2CR'})[RNH_3^+ \ ^-O_2CR'] \quad (1)$$

for the micellar catalysis, and $k_{RNH_3^+}$ and $k_{-O_2CR'}$ represent rate constants due to the alkylammonium and carboxylate groups of the surfactant, respectively. Below the critical micelle concentration, the hydrolysis is entirely due to $k_{RNH_3^+} + k_{-O_2CR'}$. The uncertainty in the precise onset of micellar catalysis as well as the possibility of catalysis by dimers, trimers, etc., do not allow meaningful calculation of the rate constants in this region. Above the critical micelle concentration, however, eq 1 is obeyed over a sufficiently large concentration range (see Table I, for example) such that k_m values can be calculated from the intercept of the extrapolated straight lines obtained on plotting k_ψ *vs.* [surfactant], and $k_{RNH_3^+} + k_{-O_2CR'}$ values can be obtained from the slopes (see Figure 1). The true values of k_m, of course, are likely to be higher than those obtained from the extrapolation.

In order to assess the relative importance of k_m, $k_{RNH_3^+}$, and $k_{-O_2CR'}$, the hydrolysis of 2,4-dinitrophenyl sulfate has been investigated in a series of alkylammonium propionates and of octylammonium carboxylates. Information on the effects of chain length in the alkylammonium and in the carboxylate group on the rate constants have been obtained from these data. For most of these surfactants, k_ψ values have only been obtained above the critical micelle concentration where they were found to be linear functions of the surfactant concentration. From the slopes and intercepts of these lines, values for $k_{RNH_3^+} + k_{-O_2CR'}$ and k_m were calculated, in a manner analogous to that indicated in Figure 1, and are given in Table II.

TABLE II

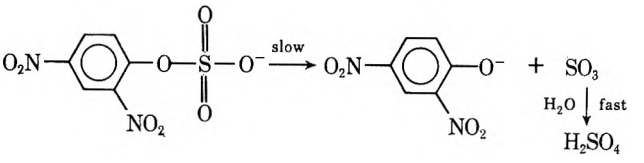
k_m AND $(k_{RNH_3^+} + k_{-O_2CR'})$ VALUES IN BENZENE IN THE PRESENCE OF ALKYLAMMONIUM CARBOXYLATE SURFACTANTS AT 24.5°

Registry no.	Surfactant	$10^4 k_m$, sec^{-1}	$10^3 (k_{RNH_3^+} + k_{-O_2CR'})$, M^{-1} sec^{-1}
17081-35-5	BAP	5.76	1.50
39107-99-8	HAP	7.37	3.32
39108-00-4	OAP	6.56	4.90
39108-01-5	DeAP	13.4	12.0
17448-65-6	DAP	9.20	18.7
	DAP[a]	23.2	99.1
41029-73-6	OAB	11.5	4.00
41029-74-7	OAN	14.3	11.6
41029-75-8	OAD	19.0	11.4
17463-35-3	OAT	16.5	9.77

[a] At 39.8°.

Rate constants for the reversed micellar catalyzed hydrolysis of 2,4-dinitrophenyl sulfate in benzene, k_m values, at 24.5° are in the range of 5.7–19 × 10^{-4} sec^{-1} (Table II). These values are 21- to 70-fold greater than that obtained for the neutral hydrolysis of 2,4-dinitrophenyl sulfate in water.[11] Although no data are available for the rate enhancement with respect to benzene, it is likely to be considerably greater than that with respect to water. Once again, therefore, catalysis of the hydrolysis of 2,4-dinitrophenyl sulfate by reversed micelles is not the sole consequence of favorable partitioning. Furthermore, the magnitude of the catalysis markedly exceeds that generally observed in "normal" micellar systems in aqueous solution. Cationic hexadecyltrimethylammonium bromide and uncharged poly(oxyethylene)(24)nonylphenol enhance the rate of neutral hydrolysis of 2,4-dinitrophenyl sulfate by factors of 3.2 and 2.6, respectively.[11]

The proposed mechanism for the hydrolysis of 2,4-dinitrophenyl sulfate in water and in aqueous micellar systems involves rate-determining sulfur–oxygen bond fission with the elimination of 2,4-dinitrophenoxide ion.[9,10] The transition state was suggested to involve



appreciable charge separation and to resemble, therefore, the hydrolysis product to a greater extent than the reactants. An essentially analogous mechanism is proposed for the hydrolysis of 2,4-dinitrophenyl sulfate in benzene in the presence of alkylammonium carboxylates. Lack of substrate solubility in pure benzene implies that the reaction site is the reversed micellar pseudophase. Based on ^{1}H nmr investigations of other solubilizates in alkylammonium carboxylate–nonpolar solvent systems,[20] it is probable that 2,4-dinitrophenyl sulfate is solubilized in the reversed micellar cavity with the anionic sulfate group and the dipolar nitro groups oriented toward the ammonium ions of the surfactants (Figure 2A). However, it is possible, but less likely, that the aromatic nucleus interacts with the hydrophobic hydrocarbon chains of the surfactant not far from the polar micellar cavity and that only the sulfate group interacts with the ammonium ions surrounding the cavity (Figure 2B). In either case, of course, the ionized sulfate group binds electrostatically to the ammonium ion. S–O bond fission is the overall result of several complex processes. Throughout the concentration range, the alkylammonium and carboxylate ions act as a general acid and a general base. Superimposed on these, above the critical micelle concentration, enhanced activity of the substrate in the micellar microenvironment relative to that in water as well as proton transfer contribute to the observed micellar catalysis. If the environment(s) of the reaction products are different from that of the reactant, as in the case of the *in situ* reactions of 2,4-dinitrophenyl sulfate in aqueous micelles,[13] then some energy is utilized for this reorganization which would otherwise be available for promoting the reaction.

Rate enhancement of 2,4-dinitrophenyl sulfate hydrolysis by DAP micelles in benzene is the combined result of substantial decreases in both the enthalpy and entropy of activation with respect to those in water (Table III). It is also apparent from Table III that the decreases in the activation enthalpy and entropy relative to water are far greater in the reversed micellar

(20) O. A. El Seoud, E. J. Fendler, and J. H. Fendler, *J. Chem. Soc., Faraday Trans. 1*, in press.

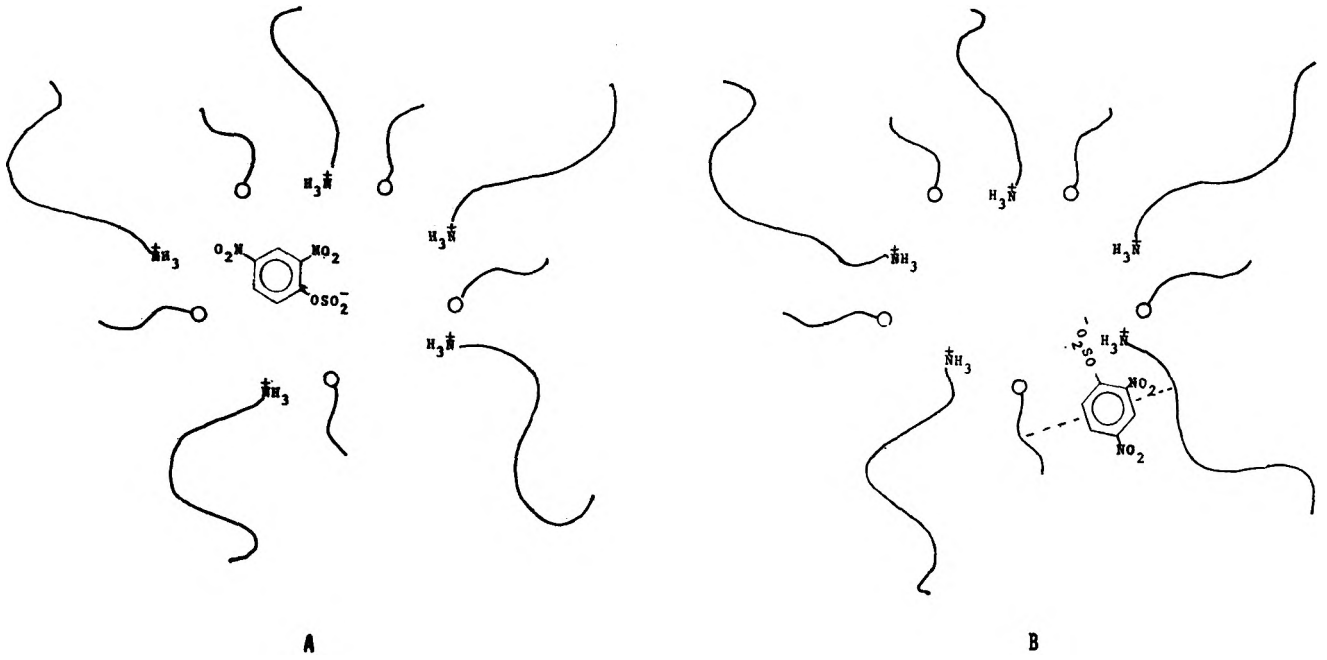


Figure 2.—Generalized schematic representation of the solubilization sites of 2,4-dinitrophenyl sulfate in reversed alkyl-ammonium carboxylate micelles.

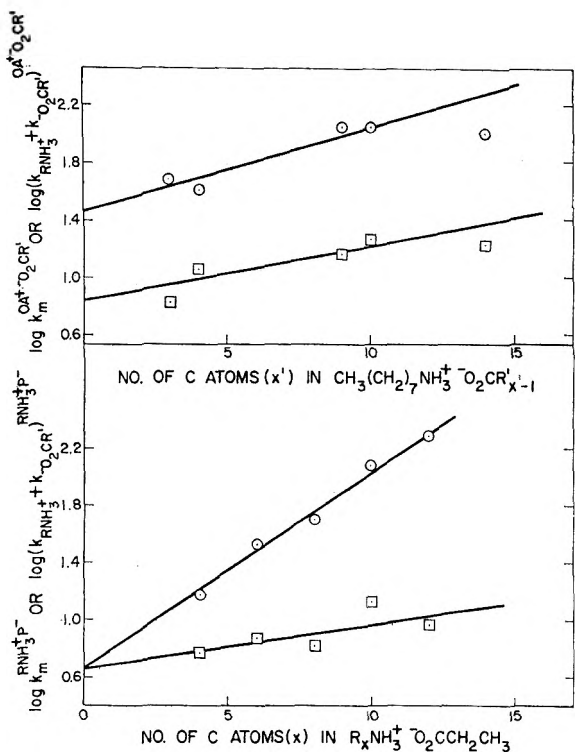


Figure 3.—The dependence of log $k_m^{RNH_3^+P^-}$ and log $k_m^{OA^+ {}^-O_2CR'}$ on the alkyl chain length x and x' (□) and of log $(k_{RNH_3^+} + k_{{}^-O_2CR'})$ on x and x' (○) at 24.5°.

system than for the "normal" hexadecyltrimethylammonium bromide (CTAB) micelles in aqueous solution. These results are compatible with the entropic argument for enzymatic catalysis proposed by Jencks[21] wherein the protein-induced concentration effect at the active site and restriction of rotational movement overcome the necessity for conformational changes in the catalyst. It is quite probable from ^1H nmr chemical

(21) M. J. Page and W. P. Jencks, *Proc. Nat. Acad. Sci.*, **68**, 1678 (1971).

Table III

Arrhenius Parameters for the Hydrolysis of 2,4-Dinitrophenyl Sulfate

Condition	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu[a]
Water[b]	18.2	−18.0
6.0×10^{-3} *M* CTAB-water[b]	16.0	−23.3
DAP-benzene, k_m	11.8	−37
DAP-benzene, $(k_{RNH_3^+} + k_{{}^-O_2CR'})$[c]	20.6	−1

[a] Calculated at 25.0°. [b] Taken from ref 11. [c] Second-order rate constant for the catalysis due to the general acid and base catalysis of DAP.

shifts and line broadening studies of solubilizates in reversed micellar systems[20] that substrates are held fairly rigidly, *i.e.*, freedom of motion is restricted, and are specifically oriented in the interior of reversed alkylammonium carboxylate micelles. Consequently, it is plausible that the remarkably large decrease in the entropy of activation (−18.0 to −37 eu, Table III) obviates or overshadows any energy requirement for structural reorganization of the micelle. These activation parameters for catalysis in reversed micellar systems as compared to those in aqueous micellar ones also suggest that the former are far superior to the latter as simple models for enzymatic catalysis.

Rate constants for the micellar catalysis, k_m, increase with increasing hydrocarbon chain length of both the alkylammonium and carboxylate groups (Table II). For the alkylammonium propionate series the relationship of eq 2 and for the octylammonium carboxylate

$$\log k_m^{RNH_3^+P^-} = \log k_m^{P^-} + ax \quad (2)$$

series the relationship of eq 3 (where $k_m^{RNH_3^+P^-}$ and

$$\log k_m^{OA^+ {}^-O_2CR'} = \log k_m^{OA^+} + bx' \quad (3)$$

$k_m^{OA^+ {}^-O_2CR'}$ are the rate constants for the alkylammonium propionate and octylammonium carboxylate micellar catalyzed reactions, respectively; $k_m^{P^-}$ and $k_m^{OA^+}$ are those due to the micellar catalysis by the propionate and the octylammonium ion, respectively;

and x and x' represent the number of carbon atoms in the alkylammonium and in the carboxylate group, respectively) is obeyed (Figure 3). From the slopes of these lines (a and b in eq 2 and 3), it is evident that changes in the chain length of the carboxylate and in the alkylammonium groups affect the micellar catalysis to the same extent. From the intercepts we calculate $k_m^{P^-} = 4.57 \times 10^{-4}$ sec^{-1} and $k_m^{OA^+} = 6.92 \times 10^{-4}$ sec^{-1}.

Equations analogous to eq 2 and 3 can be written for the dependency of $(k_{RNH_3^+} + k_{^-O_2CR'})$ on increasing chain length of alkylammonium propionates (eq 4)

$$\log (k_{RNH_3^+} + k_{^-O_2CR'})^{RNH_3^+P^-} = \log k_{P^-} + ax \quad (4)$$

and octylammonium carboxylates (eq 5) (where k_{P^-}

$$\log (k_{RNH_3^+} + k_{^-O_2CR'})^{OA^+\ ^-O_2CR'} = \log k_{OA^+} + bx' \quad (5)$$

and k_{OA^+} are the rate constants for the general base catalyzed reaction due to the propionate ion and for the general acid catalyzed reaction due to the octylammonium ion, respectively; and x and x' represent the number of carbon atoms in the alkylammonium and the carboxylate groups, respectively). Plots of the data according to eq 4 and 5 yielded good straight lines (Figure 2). It is evident that general acid catalysis is more powerful than general base catalysis. Changes in the rate per carbon atom are more than twice as great for the alkylammonium propionate series than for the octylammonium carboxylates. A qualitatively similar trend is observed for the general acid and base catalyzed hydrolyses of sulfate esters in aqueous solutions.[9,10] The values of k_{P^-} and k_{OA^+} calculated from the intercepts are 4.57×10^{-4} and $2.89 \times 10^{-3}\ M^{-1}$ sec^{-1}.

It is difficult to compare enthalpies and entropies of activation for the reaction of DAP as a general acid and a general base (Table III) directly with those obtained for the other systems, since the values for the former were obtained from composite second-order rate constants. Nevertheless, this process appears to be energetically less favorable than hydrolysis in pure water.

Acknowledgments.—This work was supported, in part, by grants from the Robert A. Welch Foundation (to J. H. F.) and the Research Corporation (to E. J. F.). C. J. O'Connor gratefully acknowledges study leave from the University of Auckland, New Zealand, a Fulbright-Hays Travel Award, and an AAUW Fellowship. E. J. Fendler is a Career Development Awardee of the National Institutes of Health, U. S. Public Health Service.

Registry No.—2,4-Dinitrophenyl sulfate, 17396-93-9.

The Hydrolysis of 3-Methoxyphthalides in Aqueous Acid. The Effect of Substituents in the 3 Position[1,2]

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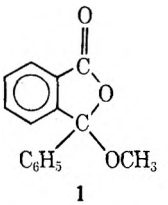
Received September 19, 1972

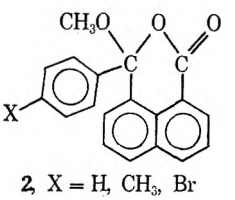
The hydrolysis of a series of 3-methoxy 3-substituted phthalides in aqueous sulfuric acid has been studied. At ~1 M acid concentration the substituents establish a relative rate order of H > CH_3 > C_6H_5 > C_2H_5 > α-naphthyl > i-C_3H_7. 3-Methoxyphthalide itself exhibits behavior consistent with a unimolecular hydrolysis mechanism when various empirical criteria such as the Zucker–Hammett hypothesis, entropy of activation, and deuterium oxide solvent isotope effect are applied. The behavior of the other compounds tends to depart from that expected from a unimolecular mechanism but can be reconciled with a unimolecular process in terms of a restriction of rotation as the molecule approaches the transition state leading to a cationic intermediate.

The hydrolysis of 3-methoxy-3-phenylphthalide[3] (1) in aqueous sulfuric acid exhibits anomalous behavior with respect to the various criteria generally used to determine the mechanisms of hydrolysis reactions in moderately concentrated mineral acid.[4] The entropy of activation (ΔS^*) was −19.4 eu, which indicated a bimolecular (A2) mechanism. However, application of the Zucker–Hammett hypothesis, the Bunnett w parameter, and the deuterium oxide solvent isotope effect all gave equivocal results. Conversely, the effect on rate of substituents in the para position of the 3-phenyl ring[5] correlated very well with σ^+ which result tends to implicate a unimolecular (A1) reaction involving a cationic intermediate at the 3 position.

These puzzling results contrast strikingly with those from the acid-catalyzed hydrolysis of 3-methoxy-3-arylperinaphthalides[6] (2). All of the empirical criteria



1



2, X = H, CH_3, Br

which were applied to the study of these compounds gave results consistent with a unimolecular reaction mechanism.

We now report the results of a study of a series of 3-methoxy 3-substituted phthalides. We believe that these results provide greater understanding of the confusing behavior of 1 and also reveal an important in-

(1) Taken from the Ph.D. Dissertation submitted by J. P. C. to Seton Hall University, 1970.

(2) Presented, in part, at Metrochem 69 Regional Meeting of the American Chemical Society, New York, N. Y., May 1969, Abstracts, p 41.

(3) In earlier publications we have named this compound as methyl pseudo-2-benzoylbenzoate. We have found that this nomenclature is unwieldy and confusing. In this and subsequent reports we shall name these compounds as phthalides.

(4) D. P. Weeks, A. Grodski, and R. Fanucci, *J. Amer. Chem. Soc.*, **90**, 4958 (1968).

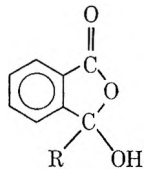
(5) D. P. Weeks and J. Cella, Abstracts, 3rd Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1968, No. H-58.

(6) D. P. Weeks and G. W. Zuorick, *J. Amer. Chem. Soc.*, **91**, 477 (1969).

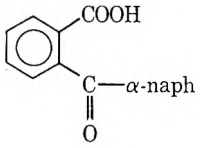
sight into a limitation of several of the empirical criteria.

Results

The 3-methoxyphthalides were prepared by esterification of the appropriate *o*-ketobenzoic acids. These acids take the cyclic (lactol) form. The one compound in this work which takes the keto acid form is *o*-α-naphthoylbenzoic acid (**7**). Compounds **3** and **4** were



3, R = H
4, R = CH_3
5, R = C_2H_5
6, R = *i*-C_3H_7



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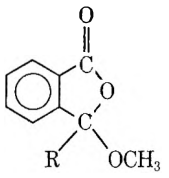


8, R = H
9, R = CH_3
10, R = C_2H_5
11, R = *i*-C_3H_7
12, R = α-naphthyl

commercially available. Compounds **5**, **6**, and **7** were prepared by allowing phthalic anhydride to react with the appropriate organocadmium. Information on the synthesis and physical properties of the *o*-ketobenzoic acids is given in Table I. Spectral data are presented in Table II.

TABLE I
SYNTHESIS AND PHYSICAL PROPERTIES OF *o*-KETOBENZOIC ACIDS

Compd (3 Substituent)	Ref	Yield,[a] %	Mp,[b] °C	Analysis,[c] % Calcd	Found
3 (H)	*d*		97.5–99		
			Lit.[e] 99		
4 (CH_3)	*d*		115–116		
			Lit.[f] 117.5		
5 (C_2H_5)	*g*	21	88–90	C 67.41	67.36
			Lit.[g] 85–88	H 5.66	5.53
6 (*i*-C_3H_7)	*g*	14	118–120	C 68.74	68.66
			Lit.[h] 120–121	H 6.29	6.47
7 (α-naphthyl)	*g*	45	171–173	C 78.25	78.27
			Lit.[g] 170–171	H 4.38	4.54

[a] After recrystallization to constant melting point. [b] Uncorrected. [c] Microanalysis by Alfred Bernhardt (Germany) or George Robertson, Florham Park, N. J. [d] Aldrich Chemical Co., Inc. [e] E. Bernatik, *Acta Chem. Scand.*, **14**, 785 (1960). [f] E. T. Harper and M. L. Bender, *J. Amer. Chem. Soc.*, **87**, 5625 (1965). [g] P. L. deBenneville, *J. Org. Chem.*, **6**, 462 (1941). [h] R. L. Letsinger and W. J. Vullo, *ibid.*, **25**, 1844 (1960).

The 3-methoxyphthalides where R = methyl and α-naphthyl (**9** and **12**) were prepared by treatment of the *o*-ketobenzoic acid with thionyl chloride followed by reaction with dry methanol containing 1 equiv of urea.[7] The others (**8**, **10**, and **11**) were prepared by allowing the keto acid to reflux in methanol which had been saturated with dry hydrogen chloride. The phthalides were separated from their isomers, the methyl *o*-ketobenzoates, by fractional crystallization. Data on the synthesis and physical properties of the phthalides are contained in Table III, and spectral data in Table IV. Two 3-methoxyphthalides and their corresponding acids, in addition to those described here, *viz.*, R = CH_2Br and R = CH_2Ph, were prepared. However, the hydrolysis of these compounds could not

(7) M. S. Newman and L. K. Lala, *Tetrahedron Lett.*, 3267 (1967).

TABLE II
SPECTRAL PROPERTIES OF *o*-KETOBENZOIC ACIDS

Compd (3 Substituent)	Infrared,[a] cm^{-1} OH	C=O	Ultraviolet,[b] nm (ε)	Chemical shift,[c] ppm (mult, no.)
5 (C_2H_5)	3310	1740	281 (1200)	0.92 (t, 3, *J* = 7.5 Hz)
			287 (1100)	2.26 (m, 2, *J* = 7.5 Hz)
				4.92 (s, 1)
				7.36–8.00 (m, 4)
6 (*i*-C_3H_7)	3310	1740	233 (9500)	0.92 (d, 3, *J* = 7 Hz)
			276 (1250)	1.07 (d, 3, *J* = 7 Hz)
			283 (1200)	2.44 (m, 1)
				4.34 (s, 1)
				7.50–8.05 (m, 4)
7 (α-naphthyl)	3050	1680	323 (74,000)	7.28–8.00 (m, 11)
		1662		9.65 (s, 1)

[a] Nujol mulls. [b] In 1 *M* aqueous sulfuric acid. [c] 10% in $CDCl_3$.

TABLE III
SYNTHESIS AND PHYSICAL PROPERTIES OF 3-METHOXYPHTHALIDES

Compd (3 Substituent)	Ref	Yield,[a] %	Mp,[b] °C	Analysis,[c] % Calcd	Found
8 (H)	*d*	50	44–45	C 65.85	65.86
			Lit.[d] 42–44	H 4.91	5.04
9 (CH_3)	*e*, *f*	18	44–45.5	C 67.41	67.54
				H 5.66	5.59
10 (C_2H_5)	*g*	19	49–51	C 68.74	68.99
			Lit.[h] 51–52	H 6.29	6.20
11 (*i*-C_3H_7)	*g*	22	47–49	C 69.89	70.04
				H 6.84	6.99
12 (α-naphthyl)	*e*, *f*	48	131–134	C 78.61	78.44
				H 4.86	4.94

[a] After recrystallization to constant melting point. [b] Uncorrected. [c] Microanalysis by Alfred Bernhardt (Germany) or George Robertson, Florham Park, N. J. [d] M. L. Bender, J. A. Reinstein, M. S. Silver, and R. Mikulak, *J. Amer. Chem. Soc.*, **87**, 4545 (1965). [e] M. S. Newman and L. K. Lala, *Tetrahedron Lett.*, 3767 (1967). [f] M. S. Newman and C. D. McCleary, *J. Amer. Chem. Soc.*, **63**, 1537 (1941). [g] K. W. Kohlransch and R. Seka, *Chem. Ber.*, **77**, 469 (1944). [h] L. K. Cresmer, A. Fischer, and J. Vaughan, *J. Chem. Soc.*, 2141 (1962).

be followed, since there was no detectable change in the ultraviolet region as the hydrolysis reaction proceeded.

Rate constants for the hydrolysis of the 3-methoxyphthalides to the keto acids were determined in various aqueous sulfuric acid solutions and are shown in Table V. Rate constants at 0.97 *M* sulfuric acid have been determined for all phthalides studied. A relative rate order of H > CH_3 > C_6H_5 > C_2H_5 > α-naphthyl > *i*-C_3H_7 has been established. Plots of the logarithms of the pseudo-first-order rate constants against the acidity function, H_0 (Zucker–Hammett hypothesis)[8] appear in Figure 1. One can see that each compound gives an excellent linear correlation. The slopes of these lines are given in Table VI. When one treats these data according to the Bunnett *w* parameter[9] the lines are severely curved, as was the line established by **1**.[4]

Activation parameters for these hydrolysis reactions and the data from which they were determined are

(8) L. Zucker and L. P. Hammett, *J. Amer. Chem. Soc.*, **61**, 2791 (1939).
(9) J. F. Bunnett, *J. Amer. Chem. Soc.*, **83**, 4956, 4968, 4973, 4978 (1961).

TABLE IV
SPECTRAL PROPERTIES OF 2-METHOXYPHTHALIDES

Compd (3 Substituent)	Infrared,[a] cm^{-1}	Ultraviolet,[b] nm (ϵ)	Chemical shift,[c] ppm (mult, no.)
8 (H)	1765	228 (9600)	3.63 (s, 3)
		272 (850)	6.34 (s, 1)
		280 (820)	7.40–8.05 (m, 4)
9 (CH_3)	1760	230 (9300)	1.84 (s, 3, CCH_3)
		272 (930)	3.07 (s, 3, OCH_3)
		281 (880)	7.35–7.98 (m, 4)
10 (C_2H_5)	1760	227 (10,500)	0.89 (t, 3, J = 7 Hz)
		273 (1050)	2.13 (m, 2, J = 7 Hz)
		280 (980)	3.05 (s, 3)
			7.35–7.98 (m, 4)
11 (i-C_3H_7)	1765	229 (9400)	0.87 (d, 3, J = 7 Hz)
		274 (1200)	1.01 (d, 3, J = 7 Hz)
		281 (1100)	2.39 (m, 1)
			3.04 (s, 3)
			7.40–8.04 (m, 4)
12 (α-naphthyl)	1760	282 (64,000)	3.37 (s, 3)
			7.15–7.26 (m, 10)
			9.05–9.80 (m, 1)

[a] Nujol mulls. [b] In methanol. [c] 10% in $CDCl_3$.

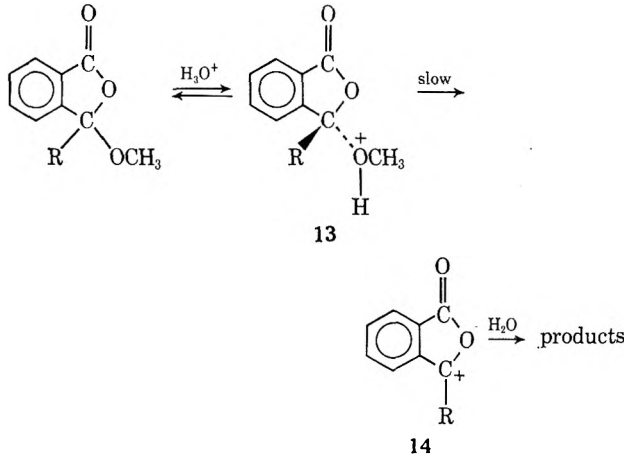
provided in Table VII. In the case of each compound a plot of the logarithm of the rate constant against the reciprocal of the absolute temperature gave a straight line.

The rate constants for the hydrolysis of these compounds were determined in solutions of sulfuric acid-d_2 and deuterium oxide in order to calculate the deuterium oxide solvent isotope effect (k_{H_2O}/k_{D_2O}). These data appear in Table VIII.

Discussion

We believe that the experimental observations on the hydrolysis of 3-methoxyphthalides can be reconciled best with an A1 mechanism (Scheme I) proceeding

SCHEME I



through a cation at the 3 position of the erstwhile phthalide. We shall set out to explain how our observations fit the mechanism in Scheme I and, in the process, attempt to eliminate alternative pathways.

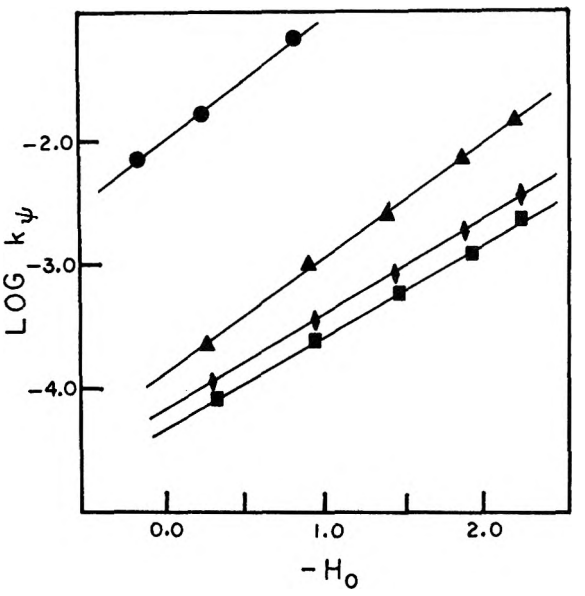


Figure 1.—Hydrolysis of 3-methoxy 3-substituted phthalides (8, ●; 9, ▲; 10, ■; 12, ◆) in sulfuric acid solutions at 25°; plot of log k_ψ against $-H_0$. The slopes are given in Table VI.

Data presented in the two papers which follow[10,11] strengthen our arguments.

In terms of the empirical criteria used in this work, 3-methoxyphthalide (8) itself is an example of reasonably well-behaved A1 hydrolysis. The slope of the straight line resulting from a plot of log k_ψ against $-H_0$ is 0.96. This value is close enough to unity to satisfy Hammett's[8] requirements for an A1 process. The value of −3.1 eu for ΔS^* is about what one would expect[12] for a mechanism involving rapid protonation followed by rate-determining unimolecular cleavage. The k_{H_2O}/k_{D_2O} of 0.51 is within the generally accepted range[13] for an A1 hydrolysis of a weakly basic substrate, albeit just on the upper border. While no one of these criteria can be depended upon to give an accurate assignment of mechanism, agreement between all three gives us confidence that the hydrolysis is a unimolecular process.

If the mechanism in Scheme I is at play it is clear that the order of relative rate of hydrolysis of 3-methoxy 3-substituted phthalides cannot be due to the inductive stabilization of the transition state leading to the cation 14. One would certainly expect that 3-methoxy-3-phenylphthalide (1) would react more rapidly than 3-methoxy-3-methylphthalide (9), which would, in turn, be faster than 8. The general trend here seems to be established by the steric bulk of the 3 substituents.

The observed decrease in reaction rate with increasing steric bulk could be due to a bimolecular mechanism in which a molecule of water attacks at C-3 as a molecule of methanol departs. Of all the alternate mechanisms, this is the most difficult to refute. We rely on the following points. First, there is a more satisfying explanation for the relative rate order and other data based on the unimolecular process in Scheme I. This is presented in the next paragraph. Second,

(10) D. P. Weeks and F. H. Field, *J. Org. Chem.*, **38**, 3380 (1973).
(11) D. P. Weeks, J. Cella, and L. T. Chen, *J. Org. Chem.*, **38**, 3383 (1973).
(12) R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **74**, 5374 (1952); R. W. Taft, Jr., E. L. Purlee, P. Riesz, and G. A. DeFazio, *ibid.*, **77**, 1584 (1955).
(13) E. H. Cordes, *Progr. Phys. Org. Chem.*, **4**, 1 (1966).

TABLE V

3-METHOXYPHTHALIDE HYDROLYSIS IN AQUEOUS SULFURIC ACID AT 25.0°

Compd (3 Substituent)	$10^4 k_\psi$,[a] sec^{-1} at [H_2SO_4] 0.49 M	0.97 M	2.04 M	3.06 M	3.99 M	4.89 M
8 (H)	70.7	153.0	599.0			
9 (CH_3)		2.88	9.19	22.8	50.1	137.0
10 (C_2H_5)		0.651	1.73	4.86	8.82	18.3
11 (i-C_3H_7)		0.0116				
12 (α-naphthyl)		0.446	1.44	3.23	7.62	18.0
1 (Ph)		0.68[b]				

[a] Average of at least two runs. [b] Extrapolated from data in ref 4.

TABLE VI

3-METHOXYPHTHALIDE HYDROLYSIS. SLOPES RESULTING FROM A PLOT OF LOG k_ψ AGAINST $-H_0$

Compd (3 Substituent)	Slope	Correlation coefficient
8 (H)	0.96	0.999
9 (CH_3)	0.80	0.998
10 (C_2H_5)	0.71	0.998
12 (α-naphthyl)	0.77	0.999
1 (Ph)	0.67[a]	

[a] Taken from ref 4.

we return to the notion that the correlation of rate with h_0 *and* a solvent isotope effect of 0.50 are not consistent with a bimolecular process and, taken together, support a unimolecular one.

Ignoring, for the moment, 3-methoxy-3-α-naphthylphthalide (**12**), one can see in Table VII that ΔS^* steadily becomes more negative as the steric bulk of the 3 substituent increases. Indeed, the enthalpies of activation (ΔH^*) for all these reactions are nearly equal and so the order of relative rate is due to the entropies. We assert that the increasingly negative ΔS^* is due to a *restriction of rotation as the molecule proceeds from the protonated form*, **13**, *to the transition state* leading to **14**. The 3 carbon in **13** is tetrahedral and the phenyl ring bisects the angle formed by the substituents R and CH_3OH^+. When CH_3OH^+ departs the 3 carbon becomes trigonal and R is required to be coplanar with the phenyl ring. Only when R = H is there no interference between R and the hydrogen atom on C-4. When R = CH_3 the van der Waals radii of R and the C-4 hydrogen overlap. Thus, free rotation of R is lost and ΔS^* becomes more negative. Compounds **10**, **1**, and **11** fit nicely into this picture. There are a number of published examples of unusually low entropies of activation allegedly caused by hindered rotation.[14-16]

3-Methoxy-3-α-naphthylphthalide (**12**) was not included in our original program of study. We prepared and investigated this compound in order to test the hypothesis in the preceding paragraph. The α-naphthyl group is so large that even in **13**, R = α-naphthyl, there is hindered rotation of R. We reasoned that this compound would have less to lose in going to **14** and would have a ΔS^* more positive than compounds such as **1** and **11**. In fact ΔS^* for **12** is -9.2 eu, that is, more positive than all the other compounds except **8**.

The simple loss of a rotational degree of freedom in the transition state for these reactions is not sufficient to account for the magnitude of ΔS^*. Humphreys and Hammett[17] have estimated that 4–6 eu may be lost owing to a restriction of rotation of a methyl group. The remaining decrease in entropy (5–7 eu) is probably caused by an increase in solvent electrostriction around the transition state. A number of authors have suggested such an effect.[15,18-23]

An unusual increase in solvation upon reaching the transition state may provide a reason why the Zucker–Hammett slopes in Table VI deviate from the expected value of 1.0. The assumption on which the Zucker–Hammett hypothesis is based is that the ratio of the activity coefficients of the substrate and the transition state must be about equal to that of a Hammett base and its conjugate acid. Unusual solvation has been shown to negate that assumption.[24-26]

The large change in ΔS^* for this series of compounds might indicate a change in mechanism from A1 to A2 as one proceeds from R = H to R = i-C_3H_7. Several observations make this unlikely. The substitution of an alkyl group for hydrogen at C-3 would tend to encourage the development of a cation at that position. A proposal of a change from A1 to A2 would require that **8** form a cation more readily than **9**. Additionally, one would expect the k_{H_2O}/k_{D_2O} value to change as the mechanism changed. Further evidence against a change in mechanism is presented in a subsequent paper.[11]

Recently a number of examples of hydrolytic reactions proceeding *via* an A-Se2 mechanism have been described.[27] Such a pathway for the 3-methoxyphthalides may be rejected on the basis of the low value of k_{H_2O}/k_{D_2O} and the absence of any detectable buffer catalysis.[4]

Note that protonation followed by unimolecular ring opening could form cation **15**. This process is also an A1 mechanism but it is less satisfying since it cannot explain the observed relative rate order. On the basis of electronic considerations one would predict a greater stability for **15**, since an $-OCH_3$ group would be better

(14) T. C. Jones and E. R. Thornton, *J. Amer. Chem. Soc.*, **89**, 4863 (1967).
(15) F. P. Price, Jr., and L. P. Hammett, *J. Amer. Chem. Soc.*, **63**, 2387 (1941).
(16) R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **75**, 4534 (1953).
(17) H. H. Humphreys and L. P. Hammett, *J. Amer. Chem. Soc.*, **78**, 521 (1956).
(18) J. E. Leffler and E. Grunwald, "Rates and Equilibrium of Organic Reactions," Wiley, New York, N. Y., 1963, p 118.
(19) L. L. Schlager and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).
(20) F. A. Long, J. G. Pritchard, and F. E. Stafford, *J. Amer. Chem. Soc.*, **79**, 2362 (1957).
(21) T. H. Fife, *J. Amer. Chem. Soc.*, **87**, 271 (1965).
(22) D. Watts, *J. Chem. Soc. B*, 543 (1968).
(23) G. Kohnstam, Transition State Symposium, Chemical Society, Special Publication No. 16, 1962, p 182.
(24) E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 237 (1963).
(25) W. M. Schubert and R. H. Quacchia, *J. Amer. Chem. Soc.*, **85**, 1278 (1963).
(26) W. M. Schubert, H. Burkett, and A. L. Schy, *J. Amer. Chem. Soc.*, **86**, 2520 (1964).
(27) T. H. Fife and L. K. Jao, *J. Amer. Chem. Soc.*, **90**, 4081 (1968); E. Anderson and T. H. Fife, *ibid.*, **91**, 7163 (1969).

TABLE VII

3-METHOXYPHTHALIDE HYDROLYSIS IN 0.97 *M* SULFURIC ACID AT VARIOUS TEMPERATURES. ACTIVATION PARAMETERS

Compd (3 Substituent)	Temp, °C	$10^4 k_\psi$, sec^{-1}	ΔH^*, kcal mol^{-1}	ΔS^*, eu
8 (H)	9.7	25.5		
	15.0	47.5		
	25.0	153.0	19.0 ± 0.2	−3.1 ± 1.0
	34.5	421.0		
9 (CH_3)	25.0	2.88	18.0 ± 0.3	−14.4 ± 1.3
	35.0	7.69		
	45.1	21.6		
	55.4	52.0		
10 (C_2H_5)	25.0	0.651	18.6 ± 0.2	−15.2 ± 1.0
	35.0	1.89		
	45.1	4.93		
	55.5	13.5		
11 (i-C_3H_7)	25.0	0.0116	19.8 ± 0.5	−19.2 ± 2.0
	35.0	0.0348		
	45.0	0.103		
12 (α-naphthyl)	25.0	0.446	20.6 ± 0.5	−9.2 ± 2.0
	35.0	1.47		
	44.0	3.77		
1 (Ph)			17.0 ± 0.3	−20.6 ± 1.3[a]

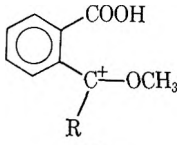
[a] Taken from ref 4. Calculated at 30.0°.

TABLE VIII

3-METHOXYPHTHALIDE HYDROLYSIS IN SOLUTIONS OF SULFURIC ACID-d_2 AND DEUTERIUM OXIDE AT 25.0°. THE DEUTERIUM OXIDE SOLVENT ISOTOPE EFFECTS

Compd (3 Substituent)	$[D_2SO_4]$, *M*	$10^4 k_\psi$,[a] sec^{-1}	k_{H_2O}/k_{D_2O}[b] ~1 *M*	k_{H_2O}/k_{D_2O}[b] ~5 *M*
8 (H)	0.97	299.0	0.51	
9 (CH_3)	0.97	5.25	0.55	
	4.89	143.0		0.96
10 (C_2H_5)	0.97	1.33	0.49	
	4.89	26.3		0.70
12 (α-Naphthyl)	0.97	0.895	0.50	
	4.89	30.8		0.58
1 (C_6H_5)			0.50[c]	0.56[c]

[a] Average of at least two runs. [b] Values for k_{H_2O} may be found in Table V. [c] Taken from ref 4.



15

able to stabilize a cation than an –OCO– would. However, the constraint of the ring will add stability to **14** by locking the cation into virtually perfect overlap with the neighboring phenyl ring. The cation is benzylic and already quite stable. This may make the difference in stabilizing effect of the two oxygen-containing groups trivial. Experimental evidence indicates that the cyclic system tends to be more stable than the ring-opened system. Thus, studies of the behavior of *o*-benzoylbenzoic acids in concentrated sulfuric acid[28] and in polyphosphoric acid[29] have indicated the cyclic cation as the preferred structure. Also, studies of the relative stabilities of pseudo (cyclic) esters and normal (ring-opened) esters of *o*-ketobenzoic acids have shown the cyclic systems to predominate at equilibrium[30] or to be kinetically favored.[31]

In Table VIII we have reported values of k_{H_2O}/k_{D_2O} at about 5 *M* acid concentration for **1**, **12**, **10**, and **9**. These are accurate and reproducible values for which we have no explanation at this time.

Finally, it is necessary to comment briefly on the fact that the hydrolysis of 3-methoxy-3-phenylperinaphthalide (**2**), which suffers hydrolysis by a pathway identical with that in Scheme I, yields an entropy of activation of 0.7 eu.[6] This molecule, with bulk around C-3 the same as that in 3-methoxy-3-phenylphthalide, does not show an effect of hindered rotation. An inspection of models shows that because of the ring geometry of the cyclic cation formed from **2** the R group is not required to lie coplanar with the naphthalene ring and there is no hindrance of rotation. We have attempted to prepare compounds of this type where R is much more bulky without success so far.

Experimental Section

Materials.—The preparation of the compounds used in this study has been summarized in the Results section and Tables I–IV. The details of these preparations were not substantially different from those in the literature and will not be repeated here.

Deuteriosulfuric acid solutions were prepared by diluting sulfuric acid-d_2 (Merck Sharp and Dohme) with deuterium oxide (Stohler Isotope Chemicals). Doubly distilled water was used for all aqueous solutions.

Rate Determinations.—The hydrolyses of the 3-methoxyphthalides were followed in the ultraviolet at 260 nm, the one exception being 3-methoxy-3-α-naphthylphthalide, which was studied at 320 nm. It was determined that all the compounds followed Beer's law in the region of concentration used (10^{-4}–10^{-5} *M*). A full spectrum of the hydrolysis run after 10 half-lives was superimposable on a spectrum of the appropriate keto acid at the same concentration. A larger sample of each 3-methoxyphthalide was allowed to hydrolyze in aqueous acid containing a suitable cosolvent. In each case the corresponding keto acid was isolated in yields of 90% or greater. The details of the kinetics method have been described previously.[4,6]

Registry No.—**1**, 7335-63-9; **3**, 16859-59-9; **4**, 1828-76-8; **5**, 40893-22-9; **5**, 6962-79-4; **7**, 5018-87-1; **8**, 4122-57-0; **9**, 1077-59-4; **10**, 40893-27-4; **11**, 40893-28-5; **12**, 40893-29-6.

(28) M. S. Newman, *J. Amer. Chem. Soc.*, **64**, 2324 (1942); M. S. Newman, H. G. Kuivila, and A. B. Garrett, *ibid.*, **67**, 704 (1945).

(29) R. G. Downing and D. E. Pearson, *J. Amer. Chem. Soc.*, **84**, 4956 (1962).

(30) P. L. deBenneville, *J. Org. Chem.*, **6**, 462 (1941).

(31) M. S. Newman and C. Courduvelis, *J. Org. Chem.*, **30**, 1795 (1965).

Chemical Ionization Mass Spectrometry. XIV. Temperature Studies of Substituted 3-Methoxyphthalides

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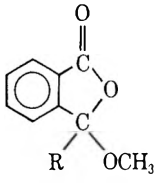
Received September 19, 1972

The temperature dependence of the methane chemical ionization mass spectra of six 3-methoxyphthalides substituted in the 3 position of the phthalide ring has been determined. The compounds studied are designated as 1–6 in the text. The major reactions occurring are loss of methanol from the protonated molecules or the loss of benzene and naphthalene from the phenyl- and α-naphthyl-substituted protonated molecules. Rate constants, activation enthalpies, and frequency factors are determined for the several decomposition reactions occurring. The rate constants for the loss of methanol decrease monotonically when the substituent on the 3 position is H, CH_3, C_2H_5, i-C_3H_7, and C_6H_5. The behavior of the α-naphthyl-substituted compound diverges from the trend. The results are basically in agreement with results previously reported in solution, and the gas-phase results are taken as a tentative corroboration of the postulate that in solution the acid-catalyzed decompositions of the several phthalides follow a unimolecular mechanism.

In the preceding[1] and subsequent papers[2] one of us (D. P. W.) reports the results of studies on the acid-catalyzed hydrolysis of 3-methoxyphthalides substituted in either the 3 position or in the 6 position of the phthalide ring. We report in this paper the results of a parallel chemical ionization study of a series of 3-methoxyphthalides substituted in the 3 position (**1**–**6**). The study was undertaken in the hope that the



1, R = H **4**, R = i-C_3H_7
2, R = CH_3 **5**, R = C_6H_5
3, R = C_2H_5 **6**, R = α-naphthyl

comparison of results obtained in gas phase and solution will serve the function of providing further knowledge about the factors influencing the gas-phase behavior and at the same time provide support for postulates made about the solution behavior.

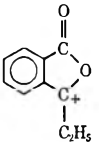
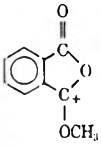
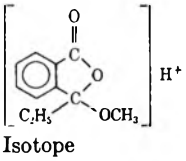
In solution the rates of the acid-catalyzed aqueous solvolysis of compounds **1**–**4** decrease monotonically in the order H > CH_3 > C_2H_5 > i-C_3H_7. The rates for R = C_6H_5 and α-naphthyl are about equal to each other and in turn about equal to the rate for R = ethyl. It is postulated[1] that the solvolyses occur by A1 mechanisms and that the substituent effect results from the occurrence of a transition state hindered rotation which varies in amount with the physical size of the substituent. The exceptional behavior of the α-naphthyl substituted compound is attributed to the occurrence of hindered rotation in both the reactant and the transition state.

A general description of chemical ionization mass spectrometry has been written,[3] and recent reports have appeared[4-7] describing the use of chemical ionization temperature studies to elucidate the physical organic chemistry of gaseous ionic systems.

Results

The mass spectra at three values of the ion source temperature for 3-ethyl-3-methoxyphthalide (**3**) using methane as reactant gas are given in Table I. Analogous spectra are obtained when the substituent at the 3 position is H, CH_3, and i-C_3H_7. The spectra of 3-phenyl-3-methoxyphthalide at three temperatures using methane as reactant gas are given in Table II, and analogous spectra are obtained when the substituent at the 3 position is α-naphthyl. The most important difference between the two types of spectra is the fact that the phenyl and α-naphthyl substituted compounds lose the arene substituent from the 3 position to form the m/e 163 ion much more readily than the other

TABLE I
CHEMICAL IONIZATION MASS SPECTRA OF 3-ETHYL-3-METHOXYPHTHALIDE (**3**). CH_4 REACTANT[a]

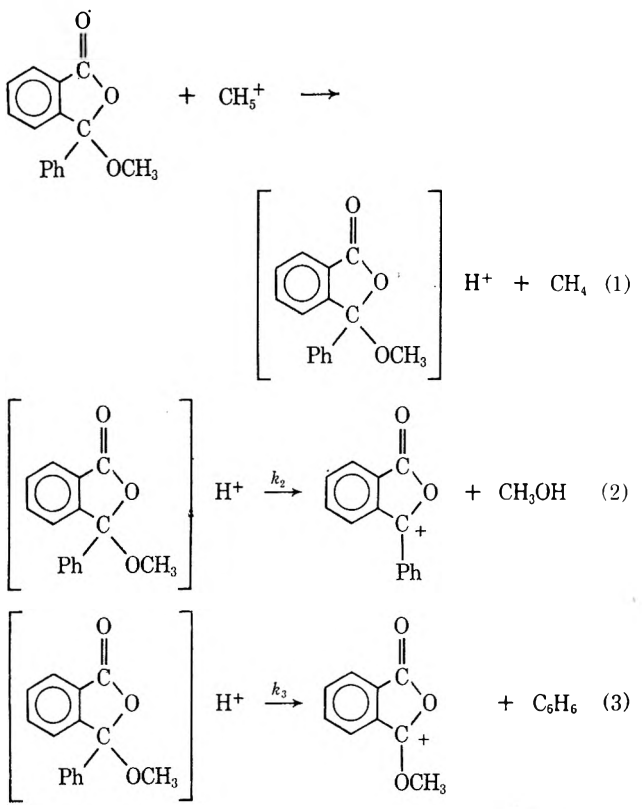
		Rel intensity at		
m/e	Ion	37°	124°	213°
105	$PhC{\equiv}O^+$	0.016	0.020	0.025
149	?	0.015	0.014	0.022
161		0.147	0.211	0.391
162	Isotope	0.016	0.031	0.045
163		0.026	0.030	0.043
193		0.566	0.457	0.295
194	Isotope	0.081	0.068	0.043
221	$(M + 29)^+$	0.083	0.085	0.048
222	Isotope	0.018	0.021	0.011
233	$(M + 41)^+$	0.030	0.030	0.019

[a] P_{CH_4} = 1.00 Torr. $P_{phthalide}$ = 10^{-4} Torr. Mol wt, 192.

(1) D. P. Weeks and J. P. Crane, *J. Org. Chem.*, **38**, 3375 (1973).
(2) D. P. Weeks, J. Cella, and L. T. Chen, *J. Org. Chem.*, **38**, 3383 (1973).
(3) F. H. Field, *Accounts Chem. Res.*, **1**, 42 (1968).
(4) F. H. Field, *J. Amer. Chem. Soc.*, **91**, 2827 (1969).
(5) F. H. Field, *J. Amer. Chem. Soc.*, **91**, 6334 (1969).
(6) D. P. Weeks and F. H. Field, *J. Amer. Chem. Soc.*, **92**, 1600 (1970).
(7) F. H. Field and D. P. Weeks, *J. Amer. Chem. Soc.*, **92**, 6521 (1970).

class of compounds loses alkyl or hydrogen to form *m/e* 163. For both types of compounds the $(M + 1)^+$ intensity is large at low temperatures and decreases as the temperature increases. On the other hand, the intensities of the ions formed by loss of methoxy (*m/e* 161 for **3**, 209 for **5**, and analogously for the other compounds) are relatively small at lower temperatures and increase as the temperature increases. For both types of compounds $(M + 29)^+$ and $(M + 41)^+$ ions are found, as is always the case with CH_4 chemical ionization, and in addition several other ions of small intensity appear in the spectra.

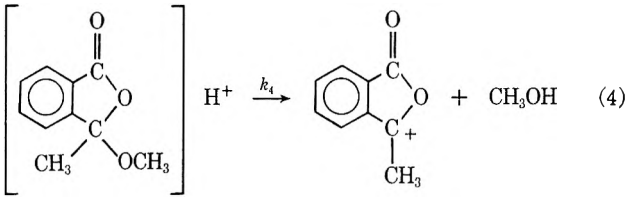
We envisage that the reactions occurring to produce the spectra involve the initial protonation of the molecule by a reactant ion from methane, and a certain fraction of these ions decompose to produce fragment ions. Thus, we write eq 1–3.



Note that, because these molecules contain several places at which a proton can be attached, we are of necessity quite noncommittal as to the actual point of attachment in eq 1–3. Obviously, however, the decomposition reactions 2 and 3 require that the proton be attached to (or migrate to) the methoxy and phenyl groups, respectively, at the time of the decompositions.

We have shown[4] that values of the rate constants k_2 and k_3 can be calculated from the intensities of the reactant and product ions in reactions such as 2 and 3, that is, from the intensities of $(M + 1)^+$ and *m/e* 209 for reaction 2 and $(M + 1)^+$ and *m/e* 163 for reaction 3.

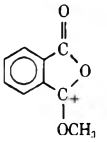
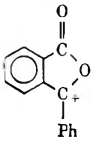
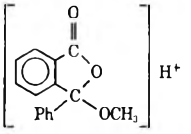
The values obtained for k_2 and k_3 depend upon temperature, and in fact the Arrhenius relationship is obeyed. This is the consequence of the fact that in the chemical ionization mass spectrometer the source pressure is high enough and sufficient collisions occur that the ion decomposition reactions such as 2 and 3 are thermally activated. The Arrhenius plot for the loss of methanol from protonated 3-methyl-3-methoxyphthalide, *i.e.*, eq 4, is given as a typical example



in Figure 1. Activation enthalpies, frequency factors, and rate constants at 300°K for the reactions analogous to 2–4 which have been studied are given in Table III. For comparison we also include in Table III the rate constants at 298° K, activation enthalpies, and activation entropies for the analogous acid-catalyzed solvolysis reactions studied by Weeks and Crane.[1]

TABLE II

CHEMICAL IONIZATION MASS SPECTRA OF 3-PHENYL-3-METHOXYPHTHALIDE (5). CH_4 REACTANT[a]

		Rel intensity at		
m/e	Ion	58°	127°	211°
105	$PhC{\equiv}O^+$	0.019	0.027	0.040
163		0.097	0.137	0.180
164	Isotope	0.015	0.015	0.020
196	?	0.015	0.020	0.018
197	?		0.016	0.016
209		0.099	0.130	0.180
210	Isotope	0.021	0.028	0.036
241		0.522	0.394	0.309
242	Isotope	0.091	0.075	0.055
263	$(M + 29)^+$	0.066	0.067	0.070
270	Isotope	0.016	0.019	0.013
281	$(M + 41)^+$	0.022	0.018	0.016

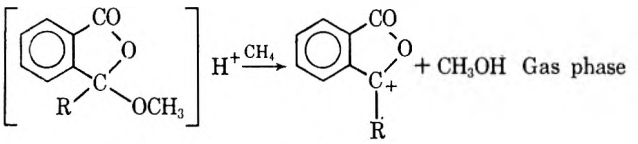
[a] P_{CH_4} = 1.00 Torr. $P_{phthalide} \cong 10^{-4}$ Torr. Mol wt, 240.

Discussion

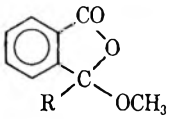
Of the three kinetic quantities given in Table III for the gas-phase reactions, the values of k_{300} are obtained by the most straightforward experimental measurements and are probably the most accurate and meaningful quantities. From Table III one observes that the k_{300} values for reactions involving compounds with R = H, CH_3, C_2H_5, and *i*-C_3H_7 undergo a monotonic decrease from 1.20×10^5 sec^{-1} to 0.35×10^5 sec^{-1}. The differences between adjacent values are small, but from an examination of the experimental data we are of the opinion that the differences are real. The rate constants for the acid-catalyzed aqueous solvolyses for these four compounds also diminish monotonically, although the magnitude of the change is much greater in the condensed-phase results than in the gas-phase results. If one carries the comparison

TABLE III

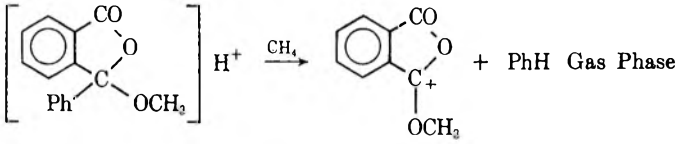
RATE QUANTITIES BY CHEMICAL IONIZATION[a] AND AQUEOUS SOLVOLYSIS[b]



R	H	CH_3	C_2H_5	i-C_3H_7	C_6H_5	α-$C_{10}H_7$
k_{300}, sec^{-1}	1.20×10^5	0.66×10^5	0.44×10^5	0.35×10^5	0.26×10^5	0.44×10^5
$\Delta H^{\ddagger}$, kcal/mol	3.5	3.8	3.2	2.8	2.9	2.3
A, sec^{-1}	4.2×10^7	4.1×10^7	1.0×10^7	0.37×10^7	0.33×10^7	0.20×10^7



k_{298}, sec^{-1}	153×10^{-4}	2.88×10^{-4}	0.65×10^{-4}	0.0116×10^{-4}	0.67×10^{-4}	0.446×10^{-4}
$\Delta H^{\ddagger}$, kcal/mol	19.0	18.0	18.6	19.8	17.0	20.6
$\Delta S^{\ddagger}$, cal/deg mol	−3.1	−14.4	−15.2	−19.2	−20.6	−9.2



k_{300}, sec^{-1}	0.34×10^5	0.31×10^5
$\Delta H^{\ddagger}$, kcal/mol	2.3	2.5
A, sec^{-1}	0.16×10^7	0.20×10^7

[a] CH_4 reactant. P_{CH_4} = 1.0 Torr. [b] Reference 1.

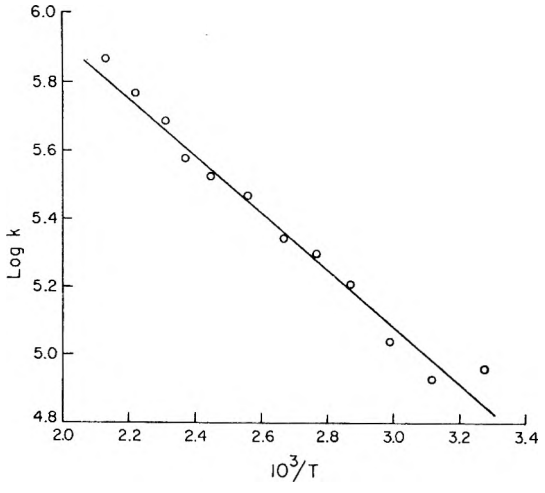


Figure 1.—Arrhenius plot for eq 4: CH_4 reactant, P_{CH_4} = 1.00 Torr.

between the gas-phase and solution results to the phenyl- and α-naphthyl-substituted compounds, one observes a divergence of behavior in that the decreasing trend is interrupted at the phenyl-substituted compound in solution but not at the α-naphthyl compound in the gas phase.

The A-factor values observed in the gas phase exhibit a monotonic decrease as the complexity of R increases, which is similar to the behavior observed in solution where ΔS^* becomes more negative in the series R = H, CH_3, C_2H_5, i-C_3H_7, and C_6H_5.

The amount of available information upon which one can base a judgment of the significance of the comparison found here between the gas-phase and solution results is very small. In total it consists of the previous findings from this laboratory that gas-phase and solution results agree well for the rates of decompositions of benzyl and *tert*-amyl acetate[4] and for methoxymethyl acetate and formate[6] but disagree for the decompositions of methylthiomethyl acetate and propionate.[7] Thus, we are obliged to present the results of Table III without extensive comment. However, we think that the qualitative trends observed in the gas phase and in solution parallel each other to such an extent that the gas-phase results may be taken as a tentative corroboration of the postulates made[1] that the acid-catalyzed decompositions of the several phthalides follow a unimolecular mechanism. Beyond that, the rather small effect of the substituent upon the decomposition rates of the gas-phase reactions is surprising, but we can offer no explanation for the phenomenon. More systems must be studied to provide an understanding of the matter.

Experimental Section

The instrumentation and procedures of chemical ionization mass spectrometry have been described elsewhere.[3,4]

The preparation of the compounds used in this study has been described by Weeks and Crane.[1]

Registry No.—1, 4122-57-0; 2, 1077-59-4; 3, 40893-27-4; 4, 40893-28-5; 5, 7335-63-9; 6, 40893-29-6.

Substituent Effects on the Hydrolysis of 3-Methoxy-3-phenylphthalides[1,2]

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Received September 19, 1972

The effect of substituents on the para position of the 3-phenyl ring on the rate of acid-catalyzed hydrolysis of 3-methoxy-3-phenylphthalides has been determined. The rates correlate with σ^+ and the reaction constant, ρ, is -1.2. The rate-enhancing effect of a methoxy group on the 6 position of the phthalide ring is more pronounced than that of a methoxy group on the para position of the 3-phenyl ring. All the compounds studied give Zucker–Hammett slopes of 0.68 ± 0.02 and rather highly negative entropies of activation and several of the compounds show deuterium oxide solvent isotope effects of $\sim$0.5. These data are consistent with an A1 hydrolysis mechanism in which hindered rotation in the transition state is a complicating factor. 3-Methoxy-3-phenyl-6-nitrophthalide suffers hydrolysis more rapidly than one would expect.

A paper[4] which precedes this one describes the unimolecular, acid-catalyzed hydrolysis of 3-methoxyphthalides having various substituents in the 3 position. It introduces an explanation for the apparently anomalous behavior of 3-methoxy-3-phenylphthalide (1) which was reported earlier.[5] We now present data on the hydrolysis of 3-methoxy-3-phenylphthalides having substituents on the para position of the 3-phenyl ring and on the 6 position of the phthalide ring. These two positions were chosen because they bear the same formal relationship to the cation which would form at the 3 position during the unimolecular (A1) hydrolysis reaction.

Results

All of the substituted 3-methoxy-3-phenylphthalides form the corresponding 2-benzoylbenzoic acid when allowed to react in aqueous mineral acid. The reactions show straightforward pseudo-first-order behavior. Psuedo-first-order rate constants (k_ψ) are shown in Table I.

Figure 1 shows a Hammett $\sigma\rho$ treatment on the rate constants determined in 1 M sulfuric acid at 30°. Rate constants for the four compounds having substituents on the para position of the 3-phenyl ring (**1–4**) correlate nicely with $\sigma^+, \rho = -1.2$. However, the rate constants for the three compounds having substituents on the 6 position (**1**, **5**, and **6**) do not correlate with either σ or σ^+ (Figure 1). The rate constants for **5** and **6** both lie above the line established by compounds **1–4**.

When log k_ψ for **1** was plotted against $-H_0$ the result was a straight line with the surprisingly small slope of 0.67.[5] Figure 2 shows the same plots for **2–6**. The slope established by each of these compounds is virtually identical with that for **1**. The actual values for the slopes are presented in Table II.

When log k_ψ is plotted against the reciprocal of the absolute temperature a straight line results. Activation parameters calculated from these plots are summarized in Table II.

The data in Table I make it possible to calculate the deuterium oxide solvent isotope effects, k_{H_2O}/k_{D_2O}, for **5** and **6**. The values are very similar to that which was established for **1**.[5]

Bunton[6] has suggested that the ratio of the rate

TABLE I

HYDROLYSIS OF SUBSTITUTED 3-METHOXY-3-PHENYLPHTHALIDES IN AQUEOUS ACID

Compd	Substituents X	Substituents Y	$[H_2SO_4]$, M	Temp, °C	$10^4 k_\psi$,[a] sec^{-1}
1	H	H	0.99	30.2	1.09 ± 0.02
			1.00[b]	30.1	0.877 ± 0.02
2	OCH_3	H	0.99	30.0	5.65 ± 0.02
			1.97	30.0	14.5 ± 0.04
			3.10	30.0	36.4 ± 0.08
			4.16	30.0	77.6 ± 0.07
			0.99	36.9	10.0 ± 0.01
			0.99	45.8	21.9 ± 0.05
3	CH_3	H	0.99	30.1	2.11 ± 0.02
			1.98	30.0	5.64 ± 0.22
			3.10	30.0	12.2 ± 0.05
			4.16	30.0	30.5 ± 0.09
			5.22	30.0	72.5 ± 0.04
			0.99	36.8	4.28 ± 0.04
			0.99	47.1	10.1 ± 0.01
4	Cl	H	0.99	29.9	0.746 ± 0.016
			1.98	30.0	1.58 ± 0.03
			3.10	30.0	4.73 ± 1.0
			4.00	30.0	10.5 ± 1.5
			5.00	30.0	21.7 ± 1.6
			0.99	37.0	1.47 ± 0.01
			0.99	47.0	3.30 ± 0.01
5	H	OCH_3	1.02	29.9	9.71 ± 0.10
			2.53	29.9	37.5 ± 0.10
			4.22	29.9	130.0 ± 1.0
			1.02	20.6	3.68 ± 0.09
			1.02	38.9	20.1 ± 0.20
			1.04[b]	29.9	7.85 ± 0.03
			1.02[c]	29.9	19.2 ± 0.20
6	H	NO_2	1.02	29.9	0.567 ± 0.005
			1.02	29.2	0.520 ± 0.009
			1.98	29.2	1.26 ± 0.01
			3.12	29.2	3.06 ± 0.02
			3.95	29.2	5.83 ± 0.21
			4.95	29.2	13.0 ± 0.20
			6.27	29.2	26.6 ± 0.90
			1.03	38.7	1.23 ± 0.01
			1.03	48.8	2.63 ± 0.07
			1.04[b]	29.9	0.463 ± 0.001
			1.02[c]	29.9	1.06 ± 0.05

[a] Average of at least two runs. Confidence intervals are based on a 95% confidence level. [b] Catalyst acid is $HClO_4$. [c] Catalyst acid is D_2SO_4.

(1) Taken, in part, from the Senior Honors Thesis submitted by J. C. to Seton Hall University, 1968, and from the M.S. Thesis submitted by L. T. C. to Seton Hall University, 1969.

(2) Presented, in part, at the Third Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1968, Abstract No. H-58.

(3) National Science Foundation Undergraduate Research Fellow, 1967–1968.

(4) D. P. Weeks and J. P. Crane, *J. Org. Chem.*, **38**, 3375 (1973).

(5) D. P. Weeks, A. Grodski, and R. Fanucci, *J. Amer. Chem. Soc.*, **90**, 4958 (1968).

(6) C. A. Bunton, J. H. Crabtree, and L. Robinson, *J. Amer. Chem. Soc.*, **90**, 1258 (1968).

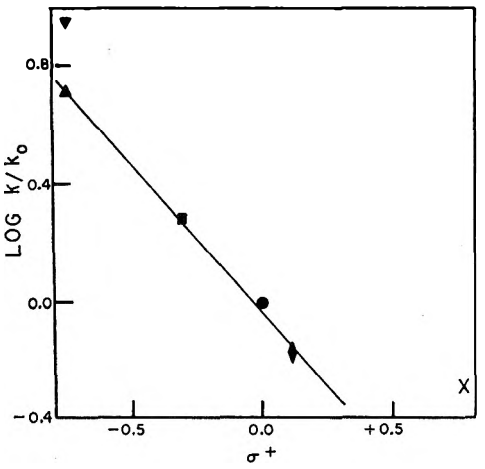


Figure 1.—Hydrolysis of substituted 3-methoxy-3-phenylphthalides: *p*-H (1), ●; *p*-OCH_3 (2), ▲; *p*-CH_3 (3), ■; *p*-Cl (4), ◆; 6-OCH_3 (5), ▼; 6-NO_2 (6), ×; plot of log k/k_0 against σ^+.

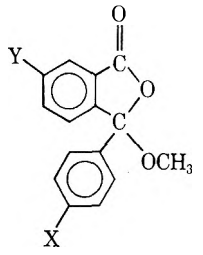
TABLE II

A SUMMARY OF EXPERIMENTAL RESULTS ON THE HYDROLYSIS OF SUBSTITUTED 3-METHOXY-3-PHENYLPHTHALIDES

Compd	Zucker–Hammett slope[a]	ΔH^*, kcal mol^{-1}	ΔS^*, eu	k_{H_2O}/k_{D_2O}	k_p/k_s[b]
1	0.67[c]	17.0[c]	−20.6[c]	0.50[c]	0.80
2	0.69	16.3	−19.7		
3	0.68	16.7	−20.1		
4	0.67	16.3	−23.7		
5	0.67	16.3	−18.5	0.50	0.81
6	0.66	15.3	−27.8	0.52	0.82

[a] Slopes of plots of log $k\psi$ against $-H_0$. [b] k_p is the rate constant in perchloric acid and k_s is the rate constant in sulfuric acid. [c] Taken from ref 5.

constants determined in perchloric acid and sulfuric acid at identical acid concentrations may distinguish between bimolecular and unimolecular hydrolysis mechanisms. These ratios for **1**, **5**, and **6** are listed in Table II.



Compd	X	Y
1	H	H
2	OCH_3	H
3	CH_3	H
4	Cl	H
5	H	OCH_3
6	H	NO_2

Discussion

The data presented here support the proposal made in the two preceding papers[4,7] that 3-methoxyphthalides suffer hydrolysis *via* an A1 pathway. The effect of substituents on the para position of the 3-phenyl ring is correlated very well by σ^+. Thus, the intermediacy of a cation at the 3 position is established.

(7) D. P. Weeks and F. H. Field, *J. Org. Chem.*, **38**, 3380 (1973).

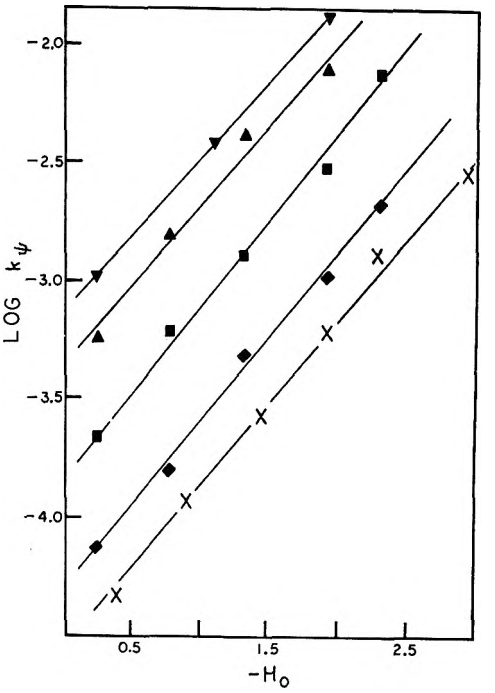


Figure 2.—Hydrolysis of substituted 3-methoxy-3-phenylphthalides: *p*-OCH_3 (2), ▲; *p*-CH_3 (3), ■; *p*-Cl (4), ◆; 6-OCH_3 (5), ▼; 6-NO_2 (6), ×; plot of log $k\psi$ against $-H_0$. The slopes are given in Table II.

The slope, $\rho = -1.2$, is not so negative as one might expect for an "acetal-like" compound. For the hydrolysis of 20 diethyl acetals and ketals,[8] ρ is −3.6, and for the hydrolysis of several diethyl acetals of meta-substituted benzaldehydes,[9] ρ is −3.35. Studies[10,11] of 2-substituted 1,3-dioxolanes give ρ values of about −4. Less negative values of σ have been obtained for the hydrolysis of 2-methyl-2-(substituted methyl)-1,3-dioxolanes[12] ($\rho = -1.48$) and 2-(substituted methyl)-2,5,5-trimethyl-1,3-dioxanes[12] ($\rho = -1.33$) but these are not strictly comparable, since the substituent is one methylene group removed from the cationic center.

We suggest that the smaller ρ value reported here is due to several factors which are not present in the systems discussed in the previous paragraph. The transition state leading to the cation is stabilized by several features, including the ring oxygen[13] and the two aryl rings. The effect of substituents will be diminished to the extent that these other features delocalize the positive charge. The only strictly comparable system on which data has been reported is the hydrolysis of 3-aryl-3-methoxyperinaphthalides[14] which correlate with σ^+ and give a ρ value of −2.1. The remaining difference of one ρ unit is consistent with our observation that the 3-phenyl ring in the phthalide system cannot lie coplanar with the developing cation and, thus, the influence of substituents on the ring will be diminished even further. In the 3-aryl-3-methoxyperinaphthalides the aryl ring at position 3 can become coplanar with the

(8) M. M. Kreevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **77**, 5590 (1955).
(9) T. H. Fife and L. K. Jao, *J. Org. Chem.*, **30**, 1492 (1965).
(10) T. H. Fife and L. Hagopian, *J. Org. Chem.*, **31**, 1772 (1966).
(11) F. Aftalion, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. Fr.*, 1497 (1965).
(12) T. C. Bruice and D. Piszkiewicz, *J. Amer. Chem. Soc.*, **89**, 3568 (1967).
(13) D. S. Noyce and R. M. Pollack, *J. Amer. Chem. Soc.*, **91**, 119 (1969).
(14) D. P. Weeks and G. W. Zuorick, *J. Amer. Chem. Soc.*, **91**, 477 (1969).

cationic center because of the puckered shape of the six-membered hetero ring in these compounds.[14] This interpretation is supported by the fact that the rate constant for 3-phenyl-3,6-dimethoxyphthalide (**5**) is greater than that for 3-*p*-anisyl-3-methoxyphthalide (**2**). That is, in **5** the methoxy group will be better able to stabilize the developing cation, since the phthalide ring to which it is attached is compelled to lie in the same plane as the cation. The fact that the rate for the 6-nitro compound is also anomalously fast is puzzling and will be discussed later in this paper.

Throughout the course of this work on the hydrolysis of 3-methoxyphthalides the possibility of a change in mechanism with changing acidity of the medium has had to be considered. That is, the marked curvature[5] of a plot of log k_ψ against log a_{H_2O} (Bunnett w)[15] might be interpreted as indicating that at low acidity the compound is undergoing hydrolysis *via* an A2 pathway and at high acidity the mechanism has changed to an A1 process. Enough examples of such things occurring in aqueous hydrolysis studies have now appeared to make it an attractive possibility.[16-18]

The evidence, taken in balance, does not support such as interpretation in this case. If the mechanism were changing from A2 to A1 as the acidity increased, then one would predict that compounds whose structure encouraged the A1 reaction by stabilizing the intermediate cation, *e.g.*, **2** and **5**, ought to suffer the change in mechanism at an acidity which is substantially lower than that at which a compound such as **1** or **4** undergoes the change. However, the w plots of all of these compounds are very similar. This similarity of the response of rate to changing acidity is illustrated more precisely by the fact that the Zucker–Hammett slopes (Table II) are virtually identical for all the compounds in this study. In addition, the almost constant value of k_{H_2O}/k_{D_2O} for compounds **1**, **5**, and **6** and the equally constant value of k_p/k_s make a change in mechanism with changing substrate structure unlikely.

The observation that the rates in sulfuric acid are faster than in perchloric acid is not predictable by Bunton's[6] reasoning. However, we have proposed[4] that unusual solvation of the transition state will be present in these reactions, and this factor could well be responsible for this aberrant behavior as well as for the breakdown of the Zucker–Hammett hypothesis. Indeed, note that it is the entropy of activation which is the important factor in determining the relative rates of substituted 3-methoxy-3-phenylphthalides. This indicates that solvation is playing an important role in the stabilization of the transition state.

Finally, there remains the question of why the hydrolysis rate of 3-methoxy-3-phenyl-6-nitrophthalide (**6**) is unusually fast. It is especially tempting to propose a change to a bimolecular mechanism in this case. The very strongly electron-withdrawing nitro group could so discourage the formation of a cation at position 3 that a bimolecular process would become possible. A nitro substituent does induce a change in mechanism in the hydrolysis of enol acetates[13] but, on the other hand, seems not to in the hydrolysis of the acetals of substituted benzaldehydes.[9] However, in the present case the deviation of **6** from the $\sigma\rho$ relationship is not accompanied by meaningful changes in the other criteria. Thus, speculation seems dangerous at the moment.

(15) J. F. Bunnett, *J. Amer. Chem. Soc.*, **83**, 4956, 4968, 4973, 4978 (1961).
(16) D. S. Noyce and R. M. Pollack, *J. Amer. Chem. Soc.*, **91**, 7158 (1969).
(17) K. Yates and R. A. McClelland, *J. Amer. Chem. Soc.*, **89**, 2686 (1967).
(18) D. P. Weeks and A. W. Levine, Abstracts, 5th Middle Atlantic Regional Meeting of the American Chemical Society, Newark, Del., April 1970, Or-17.

Experimental Section

Materials.—Deuteriosulfuric acid solutions were prepared by diluting sulfuric acid-d_2 (Merck Sharp and Dohme) with deuterium oxide (Stohler Isotope Chemicals). All sulfuric and perchloric acid solutions were standardized individually. Doubly distilled water was used for all aqueous solutions. Methanol which was freshly distilled from sodium methoxide was used in the preparation of stock solutions for the kinetics runs.

2-*p*-Anisoylbenzoic acid, 2-*p*-toluylbenzoic acid, and 2-(*p*-chlorobenzoyl)benzoic acid were prepared by a normal[19] Friedel–Crafts reaction of the appropriately substituted benzene and phthalic anhydride. Yields were greater than 75% and melting points agreed with those cited in the literature.[20,21]

5-Methoxy-2-benzoylbenzoic Acid.—A solution of 12 g of potassium permanganate, 40 ml of 5% sodium hydroxide, and 200 ml of water was allowed to react with 4 g (0.022 mol) of 2-methyl-4-methoxybenzophenone[22] by refluxing for 2 hr. The excess permanganate was destroyed by adding a few drops of ethanol and the manganese dioxide was removed by filtration. The filtrate was reduced to a volume of 50 ml and acidified with dilute sulfuric acid. The product crystallized on cooling. Upon recrystallization from benzene–ether 0.4 g (10%) of keto acid was obtained, mp 149–152° (lit.[23] mp 149–151.2°).

Anal. Calcd for $C_{15}H_{12}O_4$: C, 70.31; H, 4.69. Found: C, 70.21; H, 4.77.

5-Nitro-2-benzoylbenzoic Acid.—Powdered aluminum chloride, 5.3 g (0.04 mol), was added cautiously with cooling and stirring to 3.86 g (0.02 mol) of 4-nitrophthalic anhydride[24] in 50 ml of benzene. The mixture was stirred at room temperature for 1 hr and then brought slowly to reflux and held there for 4 hr. After the careful addition of ice and concentrated HCl the organic material was extracted with ether. The ether was removed and the yellow oil crystallized on standing overnight. Recrystallization from benzene–ether gave 1.6 g (30%) of keto acid, mp 214–215° (lit.[23] mp 213–214.2°).

Anal. Calcd for $C_{14}H_9NO_5$: C, 61.99; H, 3.32. Found: C, 62.17; H, 3.48.

Actually, two nitro-2-benzoylbenzoic acids are formed in the reaction of 4-nitrophthalic anhydride and benzene. We felt that the evidence for the isomer melting at 215° being 5-nitro-2-benzoylbenzoic acid was not completely convincing. Therefore, we established the identity of this isomer by decarboxylation.

Decarboxylation of 5-Nitro-2-benzoylbenzoic Acid.—The copper salt of the acid was prepared by allowing 0.05 g of the acid to dissolve in 7 ml of a solution of 30 ml of water containing 0.05 g of sodium hydroxide. Benzene was added and the water was removed as the azeotrope. Excess benzene was removed and the salt was redissolved in 4 ml of water. An aqueous solution of copper sulfate was added and the resulting blue precipitate was collected, washed with water, and dried in a vacuum oven. In a 10-ml flask was mixed 0.36 g of 5-nitro-2-benzoylbenzoic acid, 0.023 g of the copper salt, and 0.01 g of finely divided copper. A reflux condenser was attached and the mixture was stirred and heated to 250–270° for 1.5 hr. A yellow solid was removed from the walls of the condenser and recrystallized twice from absolute ethanol. The fine, light yellow crystals of 4-nitrobenzophenone weighed 0.06 g (21%), mp 134–136° (lit.[25] mp 138°). The ir spectrum was superimposable on that of a

(19) L. Fieser in "Organic Syntheses," Collect. Vol. IV, N. Rabjohn, Ed. Wiley, New York, N. Y., 1963, p 517.
(20) R. G. Downing and D. E. Pearson, *J. Amer. Chem. Soc.*, **84**, 4956 (1962).
(21) W. R. Orndorff and L. Kelley, *J. Amer. Chem. Soc.*, **44**, 1518 (1922).
(22) N. P. Bun-Hoi, R. Royer, and B. Eckert, *J. Org. Chem.*, **17**, 1463 (1952).
(23) D. S. Noyce and P. A. Kittle, *J. Org. Chem.*, **30**, 1899 (1965).
(24) W. A. Lawrence, *J. Amer. Chem. Soc.*, **42**, 1871 (1920).
(25) "Handbook of Chemistry and Physics," 48th ed, Chemical Rubber, Co., Cleveland, Ohio, 1967, p C-200.

genuine sample of 4-nitrobenzophenone.[26] Spectral data for all keto acids may be found in Table III.

TABLE III
SPECTRAL PROPERTIES OF o-KETOBENZOIC ACIDS

Compd	Infrared,[a] cm⁻¹ RR'C=O	Infrared,[a] cm⁻¹ COOH	Ultraviolet,[b] nm (ε)
2-*p*-Anisoylbenzoic acid	1660	1680	290 (14,400)
2-*p*-Toluylbenzoic acid	1670	1690	264 (19,850)
2-(*p*-Chlorobenzoyl)-benzoic acid	1670	1690	262 (17,200)
5-Methoxy-2-benzoyl-benzoic acid	1675	1690	253 (14,780)
5-Nitro-2-benzoyl-benzoic acid	1680	1692	263 (32,860)

[a] Nujol mulls. [b] In water.

TABLE IV
MELTING POINTS AND ANALYSES OF SUBSTITUTED 3-METHOXY-3-PHENYLPHTHALIDES

Compd	Mp,[a] °C	Analysis,[b] % Calcd	Found
2	77–80	C 70.12	70.40
	lit.[c] 80–81.5	H 5.22	5.11
3	66–67	C 75.57	75.44
	lit.[d] 71–72	H 5.55	5.46
4	100–101	C 65.58	65.82
	lit.[e] 101–102	H 4.04	4.05
5	66–68	C 71.11	71.24
		H 5.19	5.31
6	84–86	C 63.16	62.86
		H 3.86	4.01

[a] Uncorrected. [b] Microanalysis by Alfred Bernhardt, Germany. [c] V. Auwers and K. Heinz, *Ber. Bunsenges. Phys. Chem.*, **52**, 586 (1919). [d] H. Meyer, *Monatsh. Chem.*, **28**, 1236 (1907). [e] E. Egerer and H. Meyer, *ibid.*, **34**, 84 (1913).

(26) We thank Mr. Steven Szucs, a National Science Foundation Undergraduate Research Fellow, for carrying out this delicate and crucial experiment.

All of the substituted 3-methoxy-3-phenylphthalides were synthesized by allowing the appropriate keto acid to react with thionyl chloride followed by treatment with dry methanol containing 1 equiv of urea.[27] Pertinent data on each compound are given in Table IV. Spectral data are given in Table V.

TABLE V
SPECTRAL PROPERTIES OF SUBSTITUTED 3-METHOXY-3-PHENYLPHTHALIDES

Compd	Infrared,[a] cm⁻¹ (C=O)	Ultraviolet,[b] nm (ε)	Kinetics wavelength, nm
2	1765	231 (18,100)	295
3	1773	221 (19,600)	260
4	1775	224 (23,500)	260
5	1768	218 (31,350)	260
		304 (2670)	
6	1790	260 (14,340)	260

[a] Nujol mulls. [b] In water.

Rate Determinations.—The hydrolyses of 3-methoxy-3-phenylphthalides were followed in the ultraviolet at wavelengths listed in Table V. It was determined that all the compounds followed Beer's law in the region of concentration used (10^{-4}–10^{-5} *M*). A full spectrum of the hydrolysis run after 10 half-lives was superimposable on a spectrum of the product at the same concentration. A larger sample of each 3-methoxyphthalide was allowed to hydrolyze in aqueous acid containing a suitable cosolvent. In each case the corresponding keto acid was recovered in yields of 95% or greater. The details of the kinetics method have been described previously.[5,14]

Registry No.—**1**, 7335-63-9; **2**, 40893-30-9; **3**, 40893-31-0; **4**, 33433-81-7; **5**, 40893-33-2; **6**, 40893-34-3; 2-*p*-anisoylbenzoic acid, 1151-15-1; 2-*p*-toluoylbenzoic acid, 85-55-2; 2-(*p*-chlorobenzoyl)benzoic acid, 85-56-3; 5-methoxy-2-benzoylbenzoic acid, 2159-48-0; 5-nitro-2-benzoylbenzoic acid, 2159-46-8; 2-methyl-4-methoxybenzophenone, 40893-37-6; 4-nitrophthalic anhydride, 5466-84-2.

(27) V. Auwers and K. Heinz, *Ber. Bunsenges. Phys. Chem.*, **52**, 586 (1919)

A Novel Synthesis of Disubstituted Maleic Anhydrides by the Pyrolysis of 1-Ethoxy-1-alkenyl Esters of α-Keto Acids[1]

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Received March 13, 1973

The preparation of a number of 1-ethoxy-1-alkenyl esters of pyruvic acid and benzoylformic acid was accomplished by addition to the corresponding ethoxyacetylenes without the use of a mercury catalyst. Pyrolysis of the esters thus formed produced the corresponding disubstituted maleic anhydride in moderate yields. This method is a general one and has the further advantage of being a one-pot reaction. The synthesis of *n*-butylphenylmaleic anhydride (**20**) and *n*-butylmethylmaleic anhydride (**25**), in yields of 45 and 44%, respectively, is reported for the first time. The major by-products of the reactions are monosubstituted β-keto esters and the ethyl esters of the starting α-keto acids. All of the isolated products of the reactions may be explained by variations of an outlined general reaction scheme. The reactions described represent a new, and possibly the most efficient, method for the synthesis of unsymmetrically disubstituted maleic anhydrides.

Recent studies here indicated that the rearrangement of 1-ethoxy-1-alkenyl esters of carboxylic acids might be a useful route to the synthesis of monosubstituted β-keto esters. The pyrolysis of 1-ethoxyvinyl pyruvate (**1**) to ethyl acetoacetate (**2**) and carbon monoxide and of di-1-ethoxyvinyl oxalate to diethyl acetonedicarboxylate demonstrated a novel synthesis of esters of β-keto acids not substituted in the α position.[3] The thermal decomposition of a variety of 1-ethoxyvinyl esters of carboxylic acids also was shown to give initially β-keto esters which, however, underwent further reaction before isolation.[4] Subsequent studies demonstrated that the heating of the 1-ethoxyvinyl ester of

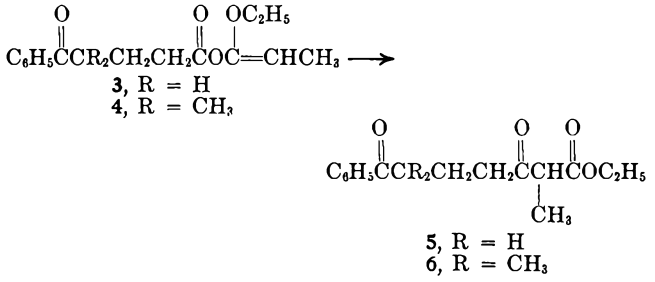
(1) This research was supported in part by Grant 12445 of the National Science Foundation.

(2) Ohio State University Postdoctoral Fellow 1971.

(3) G. R. Banks, D. Cohen, and H. D. Springall, *Rec. Trav. Chim. Pays-Bas*, **83**, 513 (1964). A repetition of this experimental procedure gave only a moderate yield of ethyl acetoacetate (see Experimental Section).

(4) B. Zwanenburg, *ibid.*, **82**, 593 (1963).

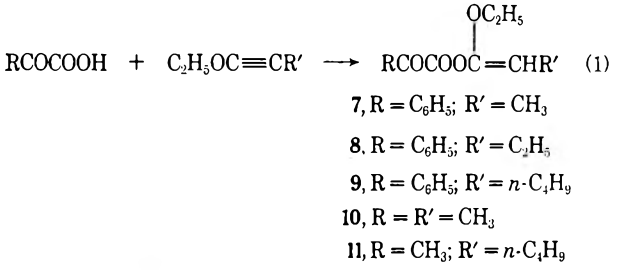
one β- and γ-keto acid did not yield any β-keto ester.[5] More recently, however, pyrolysis of 1-ethoxy-1-propenyl 4-benzoylbutanoate (**3**) and 1-ethoxy-1-propenyl 4-benzoyl-4,4-dimethylbutanoate (**4**) was shown to yield ethyl 3,7-diketo-2-methyl-7-phenyl heptanoate (**5**) and ethyl 3,7-diketo-7-phenyl-2,6,6-trimethylheptanoate (**6**),[6] respectively.



3, R = H
4, R = CH_3

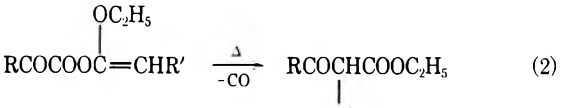
5, R = H
6, R = CH_3

Since new methods for synthesis of monsubstituted β-keto esters are of interest, we undertook a study of the formation and pyrolysis of 1-ethoxy-1-alkenyl esters of pyruvic and benzoylformic acids. The desired 1-ethoxy-1-alkenyl esters (**7**–**11**) were prepared in almost quantitative yield by the addition of the α-keto acids to 1-ethoxy-1-propyne, 1-ethoxy-1-butyne, and 1-ethoxy-1-hexyne (eq 1). Since these 1-ethoxy-1-alkenyl esters were sensitive to heat and hydrolysis, they were isolated rapidly under mild conditions and immediately pyrolyzed. Initial attempts to synthesize monosubstituted β-keto esters (**12**) by this method (eq. 2) gave poor yields (10–35%). However, an unexpected new reaction to produce disubstituted maleic anhydrides (**13**) was discovered (eq 3).



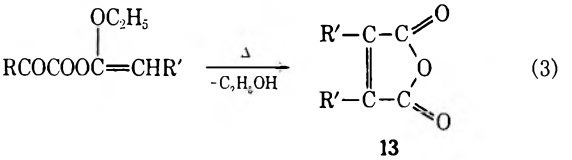
(1)

7, R = C_6H_5; R′ = CH_3
8, R = C_6H_5; R′ = C_2H_5
9, R = C_6H_5; R′ = n-C_4H_9
10, R = R′ = CH_3
11, R = CH_3; R′ = n-C_4H_9



(2)

12



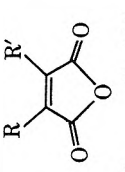
(3)

13

Since an improved method for preparing the needed 1-ethoxy-1-alkynes has been reported recently,[7] a general synthesis for disubstituted maleic anhydrides is at hand (Table I). Because other syntheses of this type of compound leave much to be desired,[8] the method described herein appears to be the method of choice to date.

(5) D. Cohen and G. E. Pattenden, *J. Chem. Soc. C*, 2314 (1967).
(6) M. S. Newman and Z. ud Din, *J. Org. Chem.*, **36**, 2740 (1971).
(7) M. S. Newman, J. R. Geib, and W. M. Stalick, *Org. Prep. Proced. Int.*, **4**, 89 (1972).
(8) J. Schreiber, *Ann. Chim. (Paris)*, **2**, 84 (1947); J. A. Moore and F. Marascia, *J. Amer. Chem. Soc.*, **81**, 6409 (1959).

TABLE I
PRODUCTS FORMED BY THE PYROLYSIS OF 1-ETHOXY-1-ALKENYL ESTERS

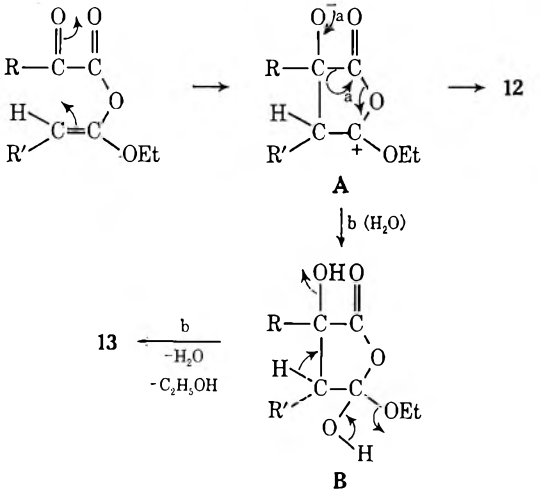
Reactants				Products									
													
R	Registry no.	R′	Catalyst	No.	% yield[a]	No.	% yield[a]	No.	% yield[a]	No.	% yield	No.	% yield[a]
C_6H_5	611-73-4	CH_3		14	41	15	4	16	14	17	1		
C_6H_5		CH_3	$Hg(OAc)_2$	14	40	15	9	16	14	17	*b*		
C_6H_5		C_2H_5		18	44	19	10	16	9				
C_6H_5	14272-91-4	C_2H_5	$Hg(OAc)_2$	18	41	19	20	16	8				
C_6H_5		n-C_4H_9		20	45	21	6	16	9	22	3		
CH_3	2806-51-1	CH_3		23	35	24	10	25	*c*				
CH_3	127-17-3	CH_3	$Hg(OAc)_2$	23	30	24	35	25	*c*				
CH_3		n-C_4H_9		25	44	26	8	25	*c*				
CH_3		H	$Hg(OAc)_2$		*b*	27	48						

[a] Based on α-keto adid. [b] A small amount was separated by vpc for identification. [c] Not isolated in pure form.

When this study was initiated, the 1-ethoxy-1-alkenyl esters (eq 1) were prepared using a mercuric acetate catalyst as had been previously described.[6,9] However, mercury contamination of the products invariably resulted despite all attempts made to remove the mercury before pyrolysis. We found that 1-ethoxy-1-alkenyl esters could be prepared in essentially quantitative yields without the mercury catalyst. Pyrolysis of mercury-free esters yielded products more easily purified for two reasons: the absence of mercury and the smaller amounts of β-keto esters present.

The formation of the products **12** and **13** by heating of **7**–**11** may be accounted for by the formation of **A** which decomposes by two paths: a, loss of carbon monoxide to yield β-keto ester (eq 2); and b, reaction with catalytic amounts of water to yield an intermediate **B** which loses ethanol to yield the disubstituted maleic anhydride (**13**).[10] The paths are shown in Scheme I.

SCHEME I



Although a mole of ethanol must be formed for every mole of **13** produced, none was isolated or detected by glpc. Examination of Table I shows two side products that were produced during the pyrolysis. The formation of these ethyl esters (**16** and **25**) of the original starting α-keto acids can be explained if one assumes that the ethanol produced from maleic anhydride formation transesterified the starting 1-ethoxy-1-alkenyl ester to produce ethyl benzoylacetate or ethyl pyruvate, and ethyl propionate, ethyl butyrate, or ethyl hexanoate, all of which were found as by-products of the reaction. Small amounts of ethyl esters were detected but insufficient to account for all of the ethanol expected. The reaction of ethanol with the ethoxyvinyl esters undoubtedly is the cause of the low yields of β-keto esters and disubstituted maleic anhydrides formed. The yields of these products might be improved if, for example, *tert*-butoxyacetylenes were used in place of ethoxyalkynes.

In summary, a number of 1-ethoxy-1-alkynes have been shown to react with α-keto acids without a mercury catalyst to give disubstituted maleic anhydrides in moderate yields. The reaction allows one to produce unsymmetrically disubstituted maleic anhydrides as easily as symmetrically substituted ones. Finally the reaction seems to be general.

(9) H. H. Wasserman and P. S. Wharton, *J. Amer. Chem. Soc.*, **82**, 661 (1960).

(10) It is realized that the timing of the steps is unknown. Hence, no attempt is made to do other than indicate the steps that may occur.

Experimental Section[11]

Reagents.—1-Ethoxy-1-propyne, 1-ethoxy-1-butyne, and 1-ethoxy-1-hexyne were prepared as described previously[7] and used immediately after distillation. Benzoylformic acid was used as received,[12] and pyruvic acid (Aldrich, Gold Label) was distilled immediately before use. Dried CH_2Cl_2 was prepared by storing over CaH_2 and distilling before use.

1-Ethoxy-1-alkenyl Esters (7–11).—These esters were all prepared by the following general method. A 500-ml round-bottomed flask equipped with a large magnetic stirring bar and a pressure-equalizing addition funnel topped with a $CaCl_2$ drying tube was half-immersed in a Dry Ice–acetone bath. Stirring was started after the addition of 50 ml of dry CH_2Cl_2. A solution of 0.375 mol of 1-ethoxy-1-alkyne in 50 ml of dry CH_2Cl_2 was added followed in 5 min by the slow addition (3 hr) of a solution of 0.15 mol of α-keto acid in 150 ml of dry CH_2Cl_2. The reaction was allowed to come to room temperature as stirring was continued overnight. The CH_2Cl_2 chloride solution was rapidly washed with an iced dilute K_2CO_3 solution followed by washing with a saturated NaCl solution. Any emulsions that were formed were dispersed by suction filtration through fine filter paper. The organic layer was percolated through anhydrous $MgSO_4$. At this point the reaction mixture was distilled at reduced pressure, keeping the bath temperature below 70°, to remove the CH_2Cl_2 and 1-ethoxy-1-alkyne which were collected together in a Dry Ice–acetone trap for later separation and recovery of the excess 1-ethoxy-1-alkyne. The 1-ethoxy-1-alkenyl esters were light yellow viscous oils that did not crystallize on standing. Since these oils were sensitive to heat and hydrolysis, they were not characterized.

General Pyrolysis Procedure of 7–11.—All of the 1-ethoxy-1-alkenyl ester obtained from 0.15 mol of α-keto acid as described in the preceding section was placed in a 50–100 ml distillation flask connected through a ground glass joint to a receiver cooled in a Dry Ice–acetone bath and connected to a vacuum pump.[13] Heating was accomplished by immersing the reaction vessel in a silicone oil bath heated to about 100°. A moderate vacuum was applied and the remnants of the 1-ethoxy-1-alkyne were removed in the first fraction. The pressure was then decreased to 0.05–0.5 mm and the bath temperature raised to 130–150° as the pyrolysis was continued for about 2 hr. The receiver was changed sometimes during this period if the head temperature indicated a change in products. If the pyrolysis was continued, small amounts of additional material continued to distil for about 3 hr more.

Pyrolysis of 1-Ethoxy-1-propenyl Benzoylformate (7).—Heating 0.15 mol of this ester as described above yielded the following compounds.

Methylphenylmaleic Anhydride (14).—This was distilled from the pyrolysis mixture at 115–128° (0.3 mm) but was contaminated with ethyl benzoylformate (**16**) and traces of the compound tentatively identified as diethyl methylphenylmaleate (**17**). The distillate crystallized upon collection and **14** was obtained as white needles by recrystallization from pentane. Distillation of the mother liquor yielded more **14**. Total yield of methylphenylmaleic anhydride was 11.0 g (41%): mp 94–4.5° (lit.[8] mp 94.5°);

(11) All melting and boiling points are uncorrected. Analyses were by M-H-W Laboratories, Garden City, Mich. Infrared spectra (samples were neat unless otherwise specified) were recorded on a Perkin-Elmer Infracord and nmr spectra on a Varian A-60 spectrometer using CCl_4 as solvent unless otherwise specified, TMS standard. Gas–liquid phase chromatographic (glpc) analyses and separations were performed on a F & M Model 500 instrument equipped with a thermal conductivity detector and using helium as a carrier gas. The separation and purification of products for identification was accomplished with a 9 ft × 3/8 in. column packed with 15% silicone gum rubber SE-30 on 60–80 mesh Chromosorb W. Identity of compounds with known compounds was established by comparison of spectra and mixture melting point determinations when applicable. All compounds had ir and nmr spectra consistent with the assigned structures. We thank Mr. Richard Weisenberger for the mass spectral determinations, which were carried out on an AEI Model AS9 instrument at an ionization potention of 70 eV.

(12) We thank the S. B. Penick Chemical Co. for a generous supply of benzoylformic acid.

(13) Similar to the apparatus described in M. S. Newman, "An Advanced Organic Laboratory Course," Macmillan, New York, N. Y., 1972, p 23.

nmr (CD_3COCD_3) δ 2.28 (s, 3, CH_3), 7.64 (m, 5, C_6H_5); ir (KBr) 5.70, 7.93, and 10.87 μ; mass spectrum *m/e* 188 (M^+),[11] 188 (M^+).

Anal. Calcd for $C_{11}H_8O_3$: C, 70.2; H, 5.3. Found: C, 70.30; H, 5.3.

Ethyl α-methylbenzoylacetate (15), contaminated with a little ethyl benzoylformate (16) as determined by glpc, was obtained in about 4% yield in the forerun of the fraction which yielded mainly 14. A sample of 15 was identified by comparison with an authentic sample: bp 94–96° (0.17 mm) [lit.[14] bp 90–94° (0.2 mm)]; nmr δ 1.15 (t, 3, CH_2CH_3), 1.42 (d, 3, $CHCH_3$), 4.12 (q, 2, OCH_2CH_3), 7.50 and 7.98 (m, 5, C_6H_5); ir 5.76, 5.92, 6.25, 6.91 μ; mass spectrum *m/e* 206 (M^+).[11]

Ethyl benzoylformate (16) was found in both of the fractions described above. Its identity was verified by comparison of a sample purified by glpc with an authentic sample made by the acid-catalyzed esterification of benzoylformic acid with ethanol.

Diethyl methylphenylmaleate (17) was found to be present as a high-boiling impurity observed as a shoulder when 14 was analyzed by glpc. A small amount of the compound tentatively identified as 17 was separated and had the following characteristics: ir 3.55, 5.75, 5.90, 6.25, 6.32, 6.85, 6.92, and 7.42 μ; mass spectrum *m/e* 262 (M^+).[11]

Pyrolysis of 1-Ethoxy-1-butenyl Benzoylformate (8).—Heating 0.15 mol of this ester as described in the general pyrolysis procedure produced a low-boiling fraction, bp 40–45° (50 mm), identified as the starting material, 1-ethoxy-1-butyne. The following compounds were isolated from succeeding fractions.

Ethylphenylmaleic anhydride (18) was one of the products isolated from the fraction boiling in the range 103–118° (25 mm). A higher boiling fraction, bp 130–135° (25 mm), yielded a dark yellow liquid that was essentially pure 18. A fractionation of the lower boiling material and a redistillation of the higher boiling fraction yielded 13.4 g (44%) of a clear light yellow liquid identified as 18. The liquid crystallized upon standing and recrystallization from ethanol yielded colorless needles: mp 43–43.5° (lit.[8] mp 43°); nmr δ 1.24 (t, 3, CH_3), 2.56 (q, 2, CH_2), and 7.52 (s, 5, C_6H_5); ir 5.67, 8.01, 10.80 (sh), and 10.92 μ; mass spectrum *m/e* 202 (M^+).[11]

Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.3; H, 5.0. Found: C, 71.1; H, 4.9.

Ethyl α-ethylbenzoylacetate (19) was one of the coproducts collected in the fraction, bp 103–118° (25 mm). Redistillation yielded a light yellow liquid analyzed by glpc to contain 2.3 g (9%) of ethyl benzoylformate (16) and 3.2 g (10%) of 19: $n^{25}D$ 1.5057 [lit.[15] bp 134–135° (3 mm)]; nmr δ 0.98 (t, 3, $CHCH_2CH_3$), 1.15 (t, 3, OCH_2CH_3), 2.00 (p, 2, $CHCH_2CH_3$), 4.13 (m, 3, OCH_2CH_3 and CH), 7.53 and 8.03 (m, 5, C_6H_5); ir 5.75, 5.91, and 6.91 μ: mass spectrum *m/e* 220 (m^+).[11]

Pyrolysis of 1-Ethoxy-1-hexenyl Benzoylformate (9).—A low-boiling fraction [bp 43–45° (8 mm)] was identified as 1-ethoxy-1-hexyne. Decreasing the pressure yielded a second fraction, bp 90–112° (0.5 mm), and left 7 g of dark tan residue.

***n*-Butylphenylmaleic anhydride (20)** was found to be present in the second fraction above, which upon redistillation yielded the following compounds: ethyl hexanoate (1.5 g), as identified by nmr and by comparison to authentic material, bp 38° (2.5 mm); and ethyl benzoylformate (16), 2.4 g (9%), bp 85–92° (1 mm). The fraction, bp 105–110° (0.5 mm), was found to be a mixture of 20 and 21 by glpc, while the highest boiling fraction, bp 110–112° (0.5 mm), was mostly 20 contaminated with a small amount of diethyl *n*-butylphenylmaleate (22). A total of 15.5 g (45%) of *n*-butylphenylmaleic anhydride (20) was isolated: $n^{25}D$ 1.5531; nmr δ 0.93 (t, 3, CH_3), 1.53 (m, 4, $CH_2CH_2CH_2CH_3$), 2.64 (t, 2, $CH_2CH_2CH_2CH_3$), 7.50 (s, 5, C_6H_5); ir 5.47, 5.70, 7.90, and 10.90 μ; mass spectrum *m/e* 230 (M^+).[11]

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.0; H, 6.1. Found: C, 73.3; H, 5.9.

Ethyl α-butylbenzoylacetate (21) was isolated from the fraction described above [bp 105–110° (0.5 mm)], as a clear, colorless liquid, 2.4 g (6%). Identification was made by comparison to an authentic sample synthesized as previously described:[16] bp 95–100° (0.6 mm); $n^{25}D$ 1.5018 (lit.[16] $n^{20}D$ 1.5044); nmr δ 0.91 (t, 3, $CH_2CH_2CH_2CH_3$), 1.13 (t, 3, OCH_2CH_3), 1.1–1.55 (m, 4, $CH_2CH_2CH_3$), 1.88 (p, 2, $CH_2CH_2CH_2CH_3$), 4.08 (q, 3, OCH_2CH_3 and CH), 7.50, and 7.95 (m, 5, C_6H_5); ir 5.72, 5.89, 6.19, and 6.82 μ; mass spectrum *m/e* 248 (M^+).[11]

Diethyl *n*-butylphenylmaleate (22) was found as a contaminant (3%) when 20 was analyzed by glpc. Separation by preparative glpc using an SE-30 column gave a small amount of material tentatively identified as 22; ir 3.38, 5.67, 5.81, 6.85, 6.95, and 7.36 μ; mass spectrum *m/e* 304 (M^+).[11]

Pyrolysis of 1-Ethoxy-1-propenyl Pyruvate (10).—A low-boiling fraction, bp 45–50° (150 mm), was identified as 1-ethoxy-1-propyne. Reducing the pressure gave another fraction, bp 40–45° (2 mm), found to contain ethyl propionate and ethyl α-methylacetoacetate (24). The third fraction, bp 60–100° (2 mm), was essentially pure ethyl propionate (3.5 g). No ethyl pyruvate (25) was isolated from the reaction mixture.

Dimethylmaleic anhydride (23), 6.7 g (35%), was distilled in essentially pure form in the final fraction [bp 100–106° (2 mm)]. The light yellow crystals were recrystallized from heptane to yield colorless plates, mp 90–92° (no depression in melting point when mixed with authentic sample from Aldrich).

Ethyl α-methylacetoacetate (24), 2.1 g (10%), was isolated mainly from the above fraction, bp 40–45° (2 mm), as a clear, colorless liquid identified by comparison to an authentic sample synthesized by a procedure similar to that of Rathke.[17]

Pyrolysis of 1-Ethoxy-1-hexenyl Pyruvate (11).—A low-boiling fraction, bp 53–56° (15 mm), was identified as 1-ethoxy-1-hexyne. A reduction in the pressure while increasing the bath temperature to 150–190° yielded a second fraction, calculated to contain 8.3 g of ethyl hexanoate and 2.2 g of 26 by glpc. Again no ethyl pyruvate was identified in the collected products.

***n*-Butylmethylmaleic anhydride (25)**, 11.2 g (44%), was collected as a pale yellow liquid, bp 110–120° (1 mm). A dark brown amorphous residue (5.7 g) that solidified upon cooling remained. Characterization of *n*-butylmethylmaleic anhyride: $n^{25}D$ 1.4677; nmr δ 0.94 (t, 3, $CH_2CH_2CH_2CH_3$), 1.5 (m, 4, $CH_2CH_2CH_2CH_3$), 2.09 (s, 3, CH_3), 2.48 (t, 2, $CH_2CH_2CH_2CH_3$); ir 5.37 (sh), 5.49 (sh), 5.62 (sh), 5.67, 7.87, 10.85, 11.24, and 13.59 μ; mass spectrum *m/e* 168 (M^+).[11]

Anal. Calcd for $C_9H_{12}O_3$: C, 64.3; H, 7.2. Found: C, 64.0; H, 7.3.

Ethyl α-butylacetoacetate (26),[16] bp 115° (16 mm), $n^{25}D$ 1.4261 (lit.[15] $n^{20}D$ 1.4288), was obtained from the fraction, bp 60–79° (1 mm), and was purified by preparative glpc: nmr δ 0.93 (t, 3, $CH_2CH_2CH_2CH_3$), 1.1–1.5 (m, 7, OCH_2CH_3 and $CH_2CH_2CH_2CH_3$), 1.73 (m, 2, $CH_2CH_2CH_2CH_3$), 3.25 (t, 1, CH), 4.16 (q, 2, OCH_2CH_3); ir 3.40, 5.73 (sh), and 5.82 μ; mass spectrum *m/e* 186 (M^+).

1-Ethoxyvinyl Pyruvate (1).—This compound was prepared essentially as described.[3,9] The dark red-brown oil obtained weighed 6.7 g (85% yield). The oil was heated for 1 hr at 90° and then distilled to give 3.8 g (48%) of a clear, colorless material, bp 65–70° (15 mm), identical with authentic ethyl acetoacetate (27) as shown by ir and nmr.

Registry No.—**7**, 40940-27-0; **8**, 40940-28-1; **9**, 40940-29-2; **10**, 40940-30-5; **11**, 40940-31-6; **14**, 41016-29-9; **15**, 10488-87-6; **16**, 1603-79-8; **17**, 40940-54-3; **18**, 40940-34-9; **19**, 24346-56-3; **20**, 40940-36-1; **21**, 6134-71-0; **22**, 40940-55-4; **23**, 766-39-2; **25**, 7541-33-5; **26**, 1540-29-0.

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Electroreduction of α,β-Unsaturated Esters. II. Syntheses of 2,3-Diaryl-5-oxocyclopentane-1-carboxylates by Hydrodimerization of Cinnamates[1a]

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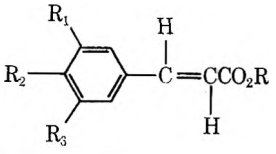
Received February 12, 1973

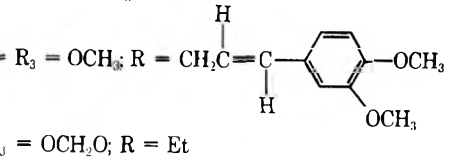
2,3-Diaryl-5-oxocyclopentane-1-carboxylates (**4**) were synthesized in yields of 7–60% by electrolytic hydrodimerization of trans cinnamate esters in anhydrous acetonitrile–tetraethylammonium bromide at constant, controlled cathode potential. For ethyl cinnamate as substrate the hydrodimer was found to have the *trans*-diphenyl geometry. A mechanism for the formation of **4**, involving steps of (a) β,β coupling of oriented anion radicals at the electrode surface, (b) protonation of the dinegative anion by an available proton source, and (c) Dieckmann-type cyclization, is suggested. When ethyl 3′,4′-dimethoxycinnamate was hydrodimerized in the presence of ethyl crotonate (nonreducible at the cathode potential used), the latter underwent concurrent catalyzed dimerization, presumably by means of acid–base interaction.

In a previous paper[2] we reported that trans cinnamate esters show two polarographic waves (presumed to involve one electron each) in anhydrous acetonitrile–tetraethylammonium bromide. Addition of a proton source (such as water) to the solvent–electrolyte caused shift of the half-wave reduction potentials to less negative values—sometimes even to the point of coalescence of the two waves into one (of twice the height). In two cases investigated, macroscale reductions conducted at a cathode potential somewhat more negative than the second (or coalesced wave) gave simple hydrogenation of the conjugated carbon–carbon double bond. We now report the results of macroscale syntheses at a cathode potential maintained between the first and second waves in the same anhydrous solvent–electrolyte.

In preparation for the electrosyntheses, polarographic investigations were conducted on a series of eight trans compounds, *viz.*, cinnamate esters **1a–f**, ethyl crotonate



1a, $R_1 = R_2 = R_3 = H$; R = Et
b, $R_1 = R_2 = R_3 = H$; R = $CH_2C{\equiv}CH$
c, $R_1 = R_2 = R_3 = H$; R = $CH_2C{\equiv}CPh$
d, $R_1 = H$; $R_2 = R_3 = OCH_3$; R = Et



e, $R_1 = H$; $R_2 = R_3 = OCH_3$; R = $CH_2C{=}C(H)$–(3,4-di-MeO-Ph)

f, $R_1 = H$; $R_2R_3 = OCH_2O$; R = Et

(2), and 3′,4′-dimethoxycinnamyl alcohol (**3**) in the aforementioned solvent system. Data are reported in Table I. From this table one notes that cinnamate esters with or without alkoxy substitutents on the phenyl ring and with either saturated or unsaturated R groups in the alcoholic moiety show two reduction waves at −1.76 to −1.94 and −2.16 to −2.31 V under anhydrous conditions. On this basis a constant cathode potential in the range of −2.06 ± 0.06 V was selected for macroscale studies on the seven esters shown in Table II. Coulometry on **1d** at −2.06 V indicated the uptake of *ca.* 1.07 electrons in the first reduction wave.

TABLE I
POLAROGRAPHIC HALF-WAVE REDUCTION POTENTIALS[a] FOR SOME MODEL COMPOUNDS

Substrate	Solvent–electrolyte[b]	First wave[c] $-E_{1/2}$	Second wave[c] $-E_{1/2}'$
1a	A	1.86	2.23
1b	A	1.77	2.16
	B	1.71	1.91
1c	A	1.76	*d*
	B	1.67	1.89
1d	A	1.94[e]	2.26[e]
1e	A	1.87	2.31
	B	1.79	2.29
1f	A	1.91	2.25
	B	1.80	2.00
2	A	2.37	*f*
3	A	2.54	*f*
	B	2.45	*f*

[a] In volts *vs.* the saturated calomel electrode. [b] A, 0.05 *M* Et_4NBr in anhydrous MeCN; B, solvent A diluted with 3.85 vol. % water. [c] Unless otherwise noted, the first and second waves have approximately equal heights. [d] Poor wave. [e] Data from ref 2. [f] No second wave is observed.

TABLE II
CYCLIC HYDRODIMERIZATION PRODUCTS FROM ELECTROREDUCTION OF TRANS CINNAMATE ESTERS IN ANHYDROUS MeCN–Et_4NBr

Cinnamate used: Aryl substituents	Cinnamate used: R group	Cinnamate used: No.	Cyclic hydrodimer formed: No.	Yield,[a] %	Mp,[a] °C
3,4-OCH_2O	Me	**1g**	**4g**	60	160–162.5
None	Et	**1a**	**4a**	52	105–106.5
None	$PhC{\equiv}CCH_2$	**1c**	**4c**[b]	8	159–161
None	*trans*-$PhCH{=}CHCH_2$	**1h**	**4h**[b]	13	126–128
3,4-di-MeO	Et	**1d**	**4d**[c]	52	110.5–112
3,4-di-MeO	*t*-Bu	**1i**	**4i**	7	118–123
3,5-di-MeO	Et	**1j**	**4j**	28	115.5–117.5

[a] Of product after one crystallization from an appropriate solvent. [b] Hydrolysis products of the substrate molecule were also isolated. [c] Dihydro-**1d** was also isolated.

It is apparent from Table I that the electrons which enter the substrate molecule are accommodated by the cinnamoyl moiety as a whole. Thus, changing the substrate from ethyl cinnamate (**1a**) to ethyl crotonate

(1) (a) This investigation was supported by Grant No. GM 12730 from the National Institute of General Medical Sciences, U. S. Public Health Service. (b) Research Assistant, 1968–1971; NDEA Fellow, 1971–1972.

(2) L. H. Klemm, D. R. Olson, and D. V. White, *J. Org. Chem.*, **36**, 3740 (1971).

(2) makes electroreduction considerably more difficult. Also the high reduction potential of 3′,4′-dimethoxycinnamyl alcohol (3) contrasts with the lower values of both $E_{1/2}$ and $E_{1/2}'$ for **1e**.

For each substrate used in these studies a crystalline cyclic hydrodimer (4) was isolated, according to balanced cathodic equation 1, where BH is a proton source (*e.g.*, Et_4N^+, CH_3CN, or even traces of H_2O). The structure of **4** was assigned to each product on the basis

$$2\mathbf{1} + 2e^- + BH \longrightarrow \mathbf{4} + OR^- + B^- \quad (1)$$

4

of elemental analyses, proton nmr spectra, the presence of two carbonyl absorption bands at 1720–1735 and 1750–1765 cm^{-1}, and a positive ferric chloride color test for the presence of an enol.[3] In addition, products **4a** and **4d** were characterized in other ways. Thus, the mass spectrum of **4d** was consistent with the proposed structure and the product was readily hydrolyzed and decarboxylated (by means of refluxing aqueous ethanolic HBr) to the corresponding 3,4-diarylcyclopentanone (**5**).

Compound **4a** has been described in the literature on two previous occasions. Totton, *et al.*,[4] obtained a 10% yield of this product by treating ethyl cinnamate with sodium under conditions of the acyloin condensation. While our studies were in progress, Baizer, *et al.*,[5] reported the formation of a mixture of products (including **4a**, ethyl β-phenylpropionate, recovered ethyl cinnamate, and diethyl 2-benzyl-3-phenylglutarate, in unstated yields) from electrolytic reduction of **1a** in aqueous DMF–tetraethylammonium *p*-toluenesulfonate. As a synthetic procedure for **4a**, electrolysis in acetonitrile appears to be the method of choice.

Hydrolytic decarboxylation of **4a** (in the foregoing manner) produced *trans*-3,4-diphenylcyclopentanone (**6**, 85% yield). Since it is unlikely that conditions of hydrolysis would cause stereochemical inversion at C-2 or C-3 in **4a**, the keto ester is also assigned the trans geometry at these two carbons (see structure **4a′**). The basic conditions attendant to the electrolytic formation of **4a** should foster equilibration at C-1. Contrariwise, these conditions should not alter the stereochemistries at C-2 and C-3. It therefore appears that the trans geometry of **4a′** is established during the process of hydrodimerization *per se*.

Baizer, *et al.*,[5] proposed that hydrodimerization may involve coupling of an anion radical with a neutral molecule. In fact his group found[6] that cross-coupling between two α,β-unsaturated esters can sometimes be effected at a cathode potential which is ostensibly too anodic to reduce directly one of the two components. In an allied experiment we electrolyzed a mixture of **1d** and ethyl crotonate (**2**) (molar ratio, 2:**1d** = 7.2:1) in anhydrous MeCN–Et_4NBr at a cathode potential of −2.03 V. Two products were isolated, *viz.*, hydrodimer **4d** and a dimer of **2**, diethyl 2-ethylidene-3-methylglutarate (**7**, 49% yield based on total **2** present or 1.7 mol of **7** per 1 mol of **1d** used). No cross-coupled products were identified. Dimer **7** has been prepared by Shabtai and Pines[7] by treatment of **2** with potassium–benzyl potassium at 110°. Under their reaction conditions they proposed that dimerization is initiated by metalation of **2** at C-2, and the attendant carbanion then undergoes Michael addition to a second molecule of **2**. In our electrolysis we favor the mechanism shown in Scheme I, where A^{2-} is an electrochemically generated

SCHEME I

$$A^{2-} + \underset{\mathbf{2}}{CH_3CH{=}CHCO_2Et} \rightleftharpoons AH^- + \bar{C}H_2CH{=}CHCO_2Et \leftrightarrow CH_2{=}C\bar{H}CHCO_2Et \quad (\mathbf{8})$$

$$\mathbf{8} + \mathbf{2} \xrightarrow{\text{Michael addition}} EtO_2CCH(CH_2{=}C(CH_3)\bar{C}HCO_2Et) \quad (\mathbf{9})$$

$$\mathbf{9} + \mathbf{2} \rightleftharpoons EtO_2CCH(CH_2{=}C(CH_3)CH_2CO_2Et) + \mathbf{8}$$

$$\mathbf{8} \text{ (proton transfer)} \uparrow\downarrow \quad EtO_2CC(CH_3){=}CHCH_2CO_2Et \quad (\mathbf{7})$$

anion (*vide infra*), which serves as initiator for a chain process of base-catalyzed dimerizations of **2** by abstraction of a γ proton from the latter. This type of mechanism was considered to represent only a "remote possibility" under the conditions used by Shabtai and Pines.

It was found that initiation of the dimerization of **2** occurs in the vicinity of the cathode and not in the bulk solution, for, when cinnamate **1d** was first hydrodimerized in the usual way and the resultant catholyte solution was then stirred with **2** (open circuit), no dimer **7** was detected. On this basis, we suggest that dimerization initiator A^{2-} is generated by a cathodic process.

Bard, *et al.*[8] offer strong evidence that the hydrodimerization of diethyl fumarate in DMF–$(n\text{-}Bu)_4NI$ (with or without added water) occurs through direct coupling of electrochemically generated anion radicals. The resultant dinegative anion is presumed to protonate rapidly. Since their findings should apply to our sys-

(3) S. Soloway and S. H. Wilen, *Anal. Chem.*, **24**, 979 (1952).

(4) E. L. Totton, R. C. Freeman, H. Powell, and T. L. Yarboro, *J. Org. Chem.*, **26**, 343 (1961).

(5) J. P. Petrovich, M. M. Baizer, and M. R. Ort, *J. Electrochem. Soc.*, **116**, 749 (1969).

(6) M. M. Baizer, J. P. Petrovich, and D. A. Tyssee, *J. Electrochem. Soc.*, **117**, 173 (1970).

(7) J. Shabtai and H. Pines, *J. Org. Chem.*, **30**, 3854 (1965). See also ref 16 for conversion of **2** to **7** by means of NaOEt in ether.

(8) W. J. Childs, J. T. Maloy, C. P. Keszthelyi, and A. J. Bard, *J. Electrochem. Soc.*, **118**, 874 (1971); V. J. Puglisi and A. J. Bard, *ibid.*, **119**, 829 (1972).

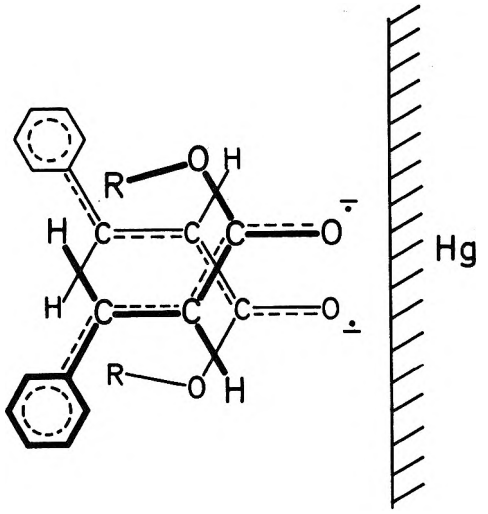
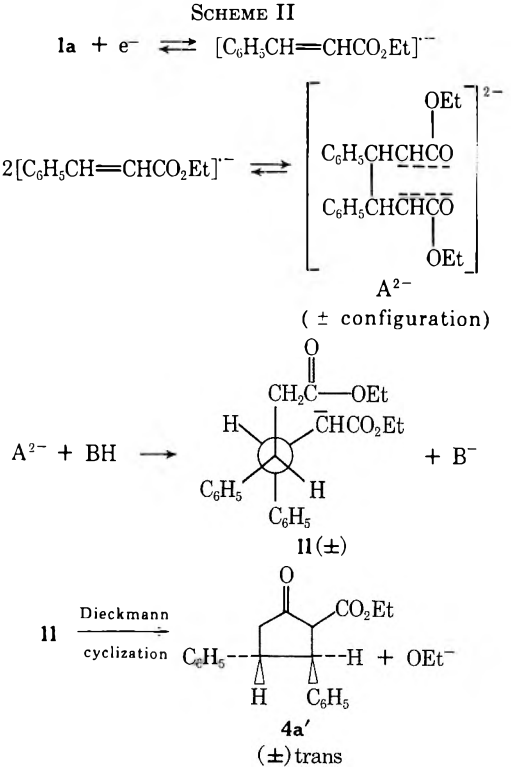


Figure 1.—Geometric relationship for β,β coupling of cinnamate ester anion radicals at the mercury cathode.

tem as well, we propose that A^{2-} is in fact the β,β-coupled product from two cinnamate ester anion radicals. The overall mechanistic scheme for the formation of cyclic hydrodimer **4a′** from ethyl cinnamate (**1a**) is then depicted in Scheme II. In this

SCHEME II



scheme, the trans stereochemistry of the final product (**4a′**) is established at the point where the two anion radicals undergo β,β coupling. Protonation on one of the α-carbon atoms gives (±) anion **11**, with the structure of an intermediate which is proposed in the familiar Dieckmann cyclization.[9] Completion of the cyclization then yields **4a′**.

It now becomes possible to rationalize the configuration of A^{2-} in terms of a preferred geometric relationship between the two reacting anion radicals. We propose that this geometry is, in fact, established between a pair of substrate molecules as they approach the electrode (*i.e.*, enter the electrical double layer adjacent to the electrode surface). While it is unnecessary that these molecules assume a preferential orientation with respect to the electrode surface itself (but only with respect to one another) in order to achieve this geometric goal, we visualize that the long axes of the cinnamate moieties approximate perpendicularity to this surface (as depicted in Figure 1). In this figure the carbonyl oxygen atoms are directed toward the electrode and approach closely enough for direct charge transfer to occur. The substrate molecules lie in close proximity in parallel planes, but with the bulky phenyl group of one molecule over the β-hydrogen atom of the other molecule. In this orientation β,β coupling could occur simultaneously with the addition of an electron to each molecule. Figure 1 shows the R groups oriented away from the electrode surface (or electrical double layer) toward the less polarizing bulk solution. In such a molecular conformation (preferred at the electrode surface, but not in the bulk solution) long or bulky R groups should interfere sterically with the close approach of the cinnamate moieties which is needed to permit β,β coupling. Thus, in a general way, Figure 1 accounts for the marked decrease in yield of cyclic hydrodimer when R is changed from Et (in **1a** or **1d**) to cinnamyl (**1h**) and phenylpropargyl (**1c**) or to *t*-Bu (**1i**), respectively. It is noteworthy that Totten[4] also obtained the trans isomer **4a′** under conditions where surface dimerization (on sodium particles) of oriented anion radicals may be invoked. It is likely that the product isolated by Baizer[5] also has the structure **4a′**.

Experimental Section[10]

Starting Materials and Apparatus.—Substrate molecules **1a–h**, **1j**, **2**, and **3** were available either commercially or from previous synthesis in our laboratory.[11,12] The acid chloride[2] from 3.11 g of *trans*-3′,4′-dimethoxycinnamic acid was stirred overnight with excess *tert*-butyl alcohol in dry benzene and the solvent was evaporated. A solution of the residue in $CHCl_3$ was washed with 10% aqueous $NaHCO_3$, dried, and evaporated to yield 3.8 g of crude, liquid ***tert*-butyl *trans*-3′,4′-dimethoxycinnamate** (**1i**), purified further by evaporative distillation at 140° (0.1 mm): ir ($CHCl_3$) 1690 (C=O) and 985 cm^{-1} (*trans*-CH=CH); pmr (CCl_4) δ 1.50 (s, 9, *t*-Bu), 3.82 (s, 6, 2 CH_3O), 6.14 (d, 1, J = 16 Hz, CH=CHC=O), 6.6–7.1 (m, 3, aromatic H), 7.46 (d, 1, CH=CHC=O).

The apparata and general procedures for polarography and macroscale synthesis at constant cathode potential were described earlier.[2] The apparatus for coulometry of 1d was modified from that used for electrosynthesis in that the Redox-O-Trol was replaced by a circuit containing a manually operated dc rheostat and a gas coulometer,[13] while the cathode potential was periodically checked by means of a potentiometer. Correction for background current was made to the coulometric reading.

Electrohydrodimerization (General Procedure).—To the catholyte of 50 ml of preelectrolyzed 0.1 M Et_4NBr in anhydrous

(9) J. P. Schaefer and J. J. Bloomfield, *Org. React.*, **15**, 1 (1967).

(10) Microanalyses were performed by Clark Microanalytical Laboratories, Urbana, Ill., M-H-W Laboratories, Garden City, Mich., and Dr. Susan Rottschaefer, University of Oregon. Infrared spectra were determined by means of a Beckman IR-5A or IR-7 spectrometer; mass spectra, by means of a CEC Model 21-110 instrument at 70 eV; and pmr spectra, by means of a Varian A-60 or HA-100 spectrometer, with tetramethylsilane as internal standard.

(11) L. H. Klemm, K. W. Gopinath, G. C. Karaboyas, G. L. Capp, and D. H. Lee, *Tetrahedron*, **20**, 871 (1964).

(12) L. H. Klemm, R. A. Klemm, P. S. Santhanam, and D. V. White, *J. Org. Chem.*, **36**, 2169 (1971).

(13) J. J. Lingane, *J. Amer. Chem. Soc.*, **67**, 1916 (1945).

MeCN was added (in one portion) 0.8–3.2 g of cinnamate ester 1 and electroreduction was conducted at a constant cathode potential of −2.06 ± 0.06 V (*vs.* a saturated calomel electrode) without external cooling of the cell until the current had fallen to background level (10–25 min). (In a few runs a solution of the ester in MeCN was added dropwise to the cathode chamber while electroreduction was proceeding, but this method gave less satisfactory results and required longer reaction times.) The catholyte and anolyte solutions were combined and evaporated. The residue was extracted with a mixture of $CHCl_3$ (or CH_2Cl_2) and water, usually 75 and 25 ml, respectively. Normally, the water layer was discarded, but, in a few cases, it was acidified to pH 1 and examined for acidic products. The dried organic layer was evaporated to give a residue which was chromatographed on a column of silica gel (3–10 g) with $CHCl_3$, EtOAc, or (in the case of **4c** only) benzene. The hydrodimer **4** was eluted in early fractions, recrystallized once to give the yield reported in Table II, and then recrystallized further to analytical purity. The hydrodimer gave a positive $FeCl_3$ test (violet)[3] and showed two carbonyl absorptions at 1720–1735 and 1750–1765 cm^{-1}. In runs with **1c** and **1h** later chromatographic effluent fractions were examined for the presence of by-products. Details on individual products are presented in subsequent paragraphs.

Methyl 2,3-Bis(3,4-methylenedioxyphenyl)-5-oxocyclopentanecarboxylate (4g).—Crystallizations of the product from methanol and ethanol gave flat prisms: mp 158–160°; ir ($CHCl_3$) 935 cm^{-1} (OCH_2O); pmr ($CDCl_3$) δ 2.5–3.0 (m, 2, 2 H-4), 3.72 (s, 3, Me) which overlaps 3.0–4.1 (m, 3, H-1, H-2, H-3), 5.90 (s, 4, 2 OCH_2O), 6.66 (broad s, 6, aromatic H).

Anal. Calcd for $C_{21}H_{18}O_7$: C, 65.96; H, 4.75. Found: C, 66.05; H, 4.75.

When the electrolysis of **1g** was conducted at 0°, only a 10% yield of **4g** was obtained.

Ethyl *trans*-2,3-Diphenyl-5-oxocyclopentanecarboxylate (4a).—The product from the CH_2Cl_2 extraction was crystallized directly (without intervening chromatography) a single time from aqueous MeOH to give fine needles: mp 105–106.5° (lit.[4] mp 102–103°, lit.[5] mp 105–107°); pmr ($CDCl_3$) δ 1.20 (t, J = 7 Hz, OCH_2CH_3), 2.6–3.0 (m, 2 H-4), 3.0–4.0 (m, H-1, H-2, H-3), 4.17 (q, OCH_2CH_3), 7.20 (s, 2 phenyl groups).

***trans*-3,4-Diphenylcyclopentanone (6).**—A solution of 115 mg of **4a** in 2 ml of EtOH and 1.3 ml of 48% HBr was refluxed for 2 hr, diluted with 10 ml of H_2O, and extracted with 25 ml of $CHCl_3$. Evaporation of the dry ($MgSO_4$) organic layer gave 75 mg (85%) of **6** as needles: mp 177–179° (lit.[14] mp 178–179° for trans isomer, 106° for cis isomer); ir ($CHCl_3$) 1745 cm^{-1}; pmr ($CDCl_3$) δ 2.3–3.0 (m, 4, 2 methylene groups), 3.2–3.6 (m, 2, H-3, H-4), 6.9–7.3 (m, 10, aromatic H), consistent with the reported[15] pmr spectrum of the trans isomer, but not with that of the cis isomer.

Ethyl 2,3-Bis(3,4-dimethoxyphenyl)-5-oxocyclopentanecarboxylate (4d).—The product was crystallized from ether and then EtOH–ether to give needles: mp 115–116°; pmr ($CDCl_3$) δ 1.23 (t, 3, J = 7 Hz, OCH_2CH_3), 2.5–3.0 (m, 2, 2 H-4), 3.74, 3.77, and 3.83 (3 s, 12, 4 MeO) plus 4.18 (q, 2, OCH_2CH_3) superimposed on 3.2–4.4 (m, 3, H-1, H-2, H-3), 6.5–6.9 (m, 6, aromatic H); mass spectrum m/e (rel intensity) 428 (82, M^+), 382 (48), 356 (15), 236 (47, $1d^+$), 191 [53, $(CH_3O)_2C_6H_3CH{=}CHC{=}O^+$], 164 [100, $(CH_3O)_2C_6H_3CH{=}CH_2^+$].

Anal. Calcd for $C_{24}H_{28}O_7$: C, 67.27; H, 6.59. Found: C, 67.49; H, 6.68.

3,4-Bis(3,4-dimethoxyphenyl)cyclopentanone (5).—Hydrolytic decarboxylation of **4d** in the manner used with **4a** and crystallization of the product from EtOH gave **5** (68%): mp 88–91°, raised to 96–97° (needles) on recrystallizations from EtOH and then from ether–petroleum ether (bp 30–60°); ir ($CHCl_3$) 1740 cm^{-1}; pmr ($CDCl_3$) δ 2.5–2.9 (m, 4, 2 CH_2 groups), 3.1–3.6 (m, 2, H-3, H-4), 3.76 and 3.83 (2 s, 6 each, 4 MeO), 6.5–6.9 (m, 6, aromatic H).

Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.76; H, 6.79. Found: C, 71.04; H, 6.81.

Ethyl 3-(3,4-Dimethoxyphenyl)propionate (10) from Electroreduction.—In an electroreduction of 0.53 g of **1d** (reaction time 70 min) the water extract was evaporated to dryness and the residue was refluxed with a mixture of 50 ml of absolute EtOH and 0.7 ml of concentrated H_2SO_4 for 5 hr. After evaporation of most of the solvent the residual solution was neutralized with aqueous $NaHCO_3$ and extracted with $CHCl_3$. Evaporation of the solvent left 120 mg (22%) of crude **10**, purified further by evaporative distillation at 100° (0.4 mm): ir ($CHCl_3$) 1730 cm^{-1}; pmr ($CDCl_3$) δ 1.23 (t, J = 7 Hz, OCH_2CH_3), 2.4–3.1 (m, CH_2CH_2), 3.85 (s, 2 MeO), 4.13 (q, OCH_2CH_3), 6.77 (s, aromatic H).

Refluxing a mixture of 100 mg of **10**, 10 mg of NH_4Cl, and 1 ml of benzylamine for 1 hr gave (after acidification and extraction into $CHCl_3$) ***N*-benzyl-3-(3,4-dimethoxyphenyl)propionamide,** obtained as needles after recrystallizations from aqueous acetone, hexane–toluene, and hexane–benzene: mp 80.5–81.5°; ir (KBr) 3280 (NH), 1640, and 1550 cm^{-1} (amide); pmr ($CDCl_3$) δ 2.3–3.1 (m, 4, CH_2CH_2), 3.76 and 3.80 (s, 6, 2 MeO), 4.35 (d, 2, J = 5.5 Hz, benzyl CH_2), 6.1–6.5 (broad, NH), 6.73 (s, 3, aromatic H of dimethoxyphenyl ring), 7.0–7.4 (m, 5, benzyl aromatic H).

Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.49; H, 6.72; N, 4.69.

Electroreduction by simultaneous addition to the catholyte of solutions of 4.4 mmol of **1d** in 25 ml of MeCN and 2.2 mmol of anhydrous HBr in 10 ml of MeCN gave **4d** (22%) and **10** (20%).

Ethyl 2,3-Bis(3,5-dimethoxyphenyl)-5-oxo-cyclopentane-1-carboxylate (4j).—This product formed clumps of needles from acetone-hexane: mp 112–113°; pmr (CCl_4) δ 1.22 (t, 3, J = 7 Hz, OCH_2CH_3), 3.66 and 3.71 (2 s, 12, 4 MeO) superimposed on 2.4–3.8 (m, 5, H-1 to H-4), 4.14 (q, 2, OCH_2CH_3), 6.1–6.4 (m, 6, aromatic H).

Anal. Calcd for $C_{24}H_{28}O_7$: C, 67.27; H, 6.59. Found: C, 67.07; H, 6.63.

***tert*-Butyl 2,3-Bis(3,4-dimethoxyphenyl)-5-oxo-cyclopentane-1-carboxylate (4i).**—This substance formed needles from ether: mp 123–124°; pmr ($CDCl_3$) δ 1.17 and 1.43 (2 s, 9, *t*-Bu), 3.75–3.95 (m, 12, 4 MeO) superimposed on 2.6–4.0 (m, 5, H-1 to H-4), 6.6–6.9 (m, 6, aromatic H).

Anal. Calcd for $C_{26}H_{32}O_7$: C, 68.40; H, 7.07. Found: C, 68.61; H, 6.91.

Phenylpropargyl 2,3-Diphenyl-5-oxo-cyclopentane-1-carboxylate (4c).—The compound crystallized as needles from MeOH: mp 164.5–165.5°; pmr ($CDCl_3$) δ 2.5–3.1 (m, 2, 2 H-4), 3.2–4.2 (m, 3, H-1, H-2, H-3), 4.96 (s, 2, $C{\equiv}CCH_2$), 7.21 (broad s, 10, phenyl groups at C-2 and C-3), 7.37 (broad s, 5, $C_6H_5C{\equiv}C$).

Anal. Calcd for $C_{27}H_{22}O_3$: C, 82.21; H, 5.62. Found: C, 82.16; H, 5.71.

The chromatographic fraction which followed **4c** off the column contained phenylpropargyl alcohol (14%), identified by spectral comparison with an authentic sample. Extraction of the acidified water layer from processing of the electroreduction mixture gave *trans*-cinnamic acid (29%), identified by mixture melting point with an authentic sample. It is uncertain at which point in the procedure these hydrolysis products are formed.

***trans*-Cinnamyl 2,3-Diphenyl-5-oxo-cyclopentane-1-carboxylate (4h).**—This compound formed needles on repetitive crystallizations from ether: mp 128–129°; ir ($CHCl_3$) 965 cm^{-1} (trans CH=CH); pmr ($CDCl_3$) δ 2.6–3.0 (m, 2, 2 H-4), 3.2–4.1 (m, 3, H-1, H-2, H-3), 4.79 (d, 2, J = 5 Hz, cinnamyl CH_2), 5.8–6.9 (m, 2, 2 vinyl H), 7.21 (broad s, 10, phenyl groups at C-2 and C-3), 7.32 (broad s, 5, $C_6H_5CH{=}$).

Anal. Calcd for $C_{27}H_{24}O_3$: C, 81.79; H, 6.10. Found: C, 81.93; H, 6.00.

As in the preparation of **4c**, hydrolysis by-products of *trans*-cinnamyl alcohol (50%) and *trans*-cinnamic acid (24%) were isolated and identified.

Electroreduction of 1d in the Presence of Ethyl Crotonate (2).—After preelectrolysis (at −2.03 V) of a mixture of the usual catholyte plus 4.1 g (36 mmol) of **2**, electroreduction was continued at the same potential while a solution of 1.19 g (5 mmol) of **1d** in 15 ml of MeCN was added (over a period of 15 min) and for 5 min longer. The total solution was evaporated, the residue was extracted with CH_2Cl_2–H_2O, and the product from evaporation of the organic phase was chromatographed on silica gel with successive elution by (a) hexane, (b) 5% $CHCl_3$ in hexane, (c) benzene, and (d) ether. Pmr analysis of effluents a and b indicated that only aliphatic protons were present. Rotary evaporation at 80° of combined effluents a and b to constant weight (compound **2** is volatile under these conditions) gave 2.02 g (49%, based on total **2** used) of **diethyl 2-ethylidene-3-methylglutarate (7):** ir ($CHCl_3$) 1640 (conjugated C=C), 1710, and 1730 cm^{-1} (ester C=O groups); pmr (neat) δ 1.17

(14) D. Y. Curtin and S. Dayagi, *Can. J. Chem.*, **42**, 867 (1964); H. A. Weidlich, *Ber.*, **71**, 1601 (1938).

(15) A. Warshawsky and B. Fuchs, *Tetrahedron*, **25**, 2633 (1969).

and 1.25 (2 overlapping t, superimposed on d, 9, 2 OCH_2CH_3 plus CH_3CHCH_2), 1.82 (d, 3, J = 7 Hz, $=CHCH_3$), 2.58 and 2.62 (2 overlapping d, 2, J = 7–8 Hz, $CH_2C=O$), 3.3 (m, 1, methinyl H), 4.05 and 4.15 (2 overlapping q, 4, J = 6–7 Hz, 2 OCH_2CH_3), 6.81 (q, 1, vinyl H); mass spectrum m/e (rel intensity) 228 (7, M^+), 183 (90, $M - C_2H_5O$), 182 (93), 155 (21), 154 (100), 140 (18), 126 (57), 125 (20), 113 (27), 112 (27), 95 (27), 81 (33), 69 (22), 67 (39), 53 (16).

Saponification of **7** gave **2-ethylidene-3-methylglutaric acid** as needles from benzene–hexane, mp 129–130° (lit.[16] mp 129°).

Anal. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.79; H, 7.09.

From chromatographic effluent d was isolated **4d** (31%).

When this electroreduction experiment was repeated in exactly the same way except that the ethyl crotonate was only stirred with the catholyte (open circuit) for 23 min after reduction of **1d** (alone) was complete, there resulted **4d** (25%) but no **7**.

(16) H. von Pechmann, *Ber.*, **33**, 3323 (1900).

Acknowledgment.—The authors wish to thank Dr. Henning Lund of Aarhus University, Denmark, and Dr. Lennart Eberson of the University of Lund, Sweden, for discussions of mechanistic aspects of this research.

Registry No.—**1a**, 4192-77-2; **1b**, 29584-63-2; **1c**, 40918-86-3; **1d**, 24393-65-5; **1e**, 40918-88-5; **1f**, 24393-66-6; **1g**, 40918-96-5; **1h**, 40918-97-6; **1i**, 40918-98-7; **1j**, 29584-64-3; **2**, 623-70-1; **3**, 40918-90-9; **4a**, 40918-91-0; **4c**, 40918-92-1; **4d**, 41021-30-1; **4g**, 40918-93-2; **4h**, 40918-94-3; **4i**, 40918-95-4; **4j**, 40919-00-4; **5**, 40919-01-5; **6**, 13351-28-5; **7**, 18418-07-0; **10**, 5462-13-5; benzylamine, 100-46-9; *N*-benzyl-3-(3,4-dimethoxyphenyl)-propionamide, 40958-49-4; 2-ethylidene-3-methylglutaric acid, 40919-04-8.

Condensation–Cyclization Reactions of Electron-Deficient Aromatics. VII. The Kinetics and Mechanism of Carbanionic σ-Complex Formation and Cyclization

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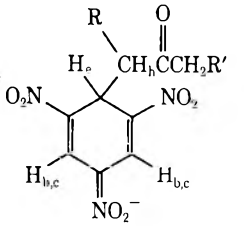
Received April 26, 1973

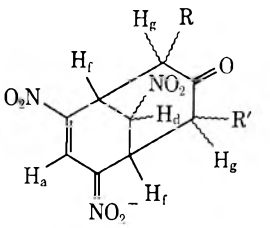
The kinetics and mechanism of formation and cyclization of the anionic σ complex obtained from the reaction of *sym*-trinitrobenzene and dibenzyl ketone are described. The reaction sequence is likely typical of a variety of similar condensation–cyclization reactions of electron-deficient aromatics with carbanions. Very rapid formation of anionic σ complex is followed by slow cyclization to bicyclic nitropropene nitronate.

Anionic σ complexes have been the subject of numerous thermodynamic and kinetic studies, both as metastable intermediates in aromatic nucleophilic substitution reactions and as products of aromatic addition. Much of this work has been summarized in several reviews.[1–5] The factors which govern the stability of such species and the way in which they are formed are now well known for a variety of different systems. In addition, the recently reported kinetic characterization of an observable metastable anionic σ complex intermediate in aromatic nucleophilic substitution in the naphthalene series[6] substantiates many early steady-state kinetic studies which had provided evidence for similar intermediates.[7–9] The resurgent interest in thermodynamic and kinetic characterizations of σ complexes of a variety of organic and inorganic bases with electron-deficient aromatics has provided considerable evidence substantiating the structure of these species and the way in which they form and decompose.

During the past 4 years, it has become clear that many carbanionic σ complexes, **1**, are unstable, not with regard to formation of a substitution product (which would require hydride expulsion), but because they readily undergo an internal cyclization reaction to yield the stable bicyclic nitropropene nitronate salts, **2**.[10–21]



1a, R = R′ = C_6H_5
b, R = R′ = -(CH_2CH_2)-
c, R = R′ = CH_3
d, R = R′ = H



2a, R = R′ = C_6H_5 (trans)
b, R = R′ = C_6H_5 (cis-endo)
c, R = R′ = C_6H_5 (cis-exo)

Isolation of intermediates, as well as qualitative visible and pmr spectral studies of the reaction, has provided evidence for two distinct cyclization mecha-

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nisms when amines are used to catalyze the formation of structures like 2 from potential bis carbanions and *sym*-trinitrobenzene (TNB).[12,13,15-17] These are shown in Schemes I and II.

SCHEME I[a]

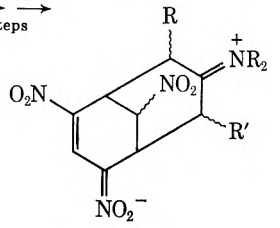
$$TNB + RCH_2COCH_2R' + NR_3 \xrightarrow[\text{steps}]{\text{(fast) several}} \mathbf{1},\ \overset{+}{H}NR_3$$

$$\mathbf{1} \xrightarrow{\text{slow}} \mathbf{2}$$

[a] R and/or R′ of ketone are electron withdrawing or delocalizing. Reaction does not proceed when these groups are electron donating (*i.e.*, alkyl or H).

SCHEME II[a]

$$TNB + RCH_2COCH_2R' + HNR_2 \xrightarrow[\text{steps}]{\text{several}} \mathbf{3}$$



$$H_2O + \mathbf{3} \longrightarrow \mathbf{2},\ \overset{+}{H_2}NR_2$$

[a] R and/or R′ of ketone are electron withdrawing *or* donating.

The qualitative evidence for these two mechanistic routes has been discussed in earlier papers,[11-13,15] and a preliminary kinetic study of the *tertiary* amine catalyzed cyclization of **1a** has been published.[16] We report here a detailed kinetic study of the fast condensation step and slow cyclization step of the tertiary amine catalyzed reaction represented in Scheme I, and propose detailed mechanisms for these steps which are likely typical for condensation–cyclization reactions of electron-deficient aromatics with acidic ketones or keto esters.

The reaction of dibenzyl ketone (DBK) and TNB in DMSO in the presence of triethylamine is particularly well suited for study. The reaction occurs in two stages, as shown in Scheme I, and the spectral characteristics of the intermediate σ complex and the product, as well as the relative rates of the two steps, are favorable for kinetic analysis by stopped flow and conventional spectrophotometric methods. In addition, the detailed product analysis published earlier for this system,[11] which showed that only a single bicyclic product forms in DMSO, has been confirmed in the present study. This observation simplifies kinetic analysis of the cyclization step considerably. A complete study of the DBK–TNB–NEt_3 system provides evidence that the proposed mechanism in this instance is similar to condensation–cyclization reactions of electron-deficient aromatics with a variety of acidic ketones and keto esters. Our observations will be shown to be consistent with the detailed mechanism illustrated in Scheme III.

Results

General Features of the Reaction.—Adding excess triethylamine to an equimolar solution of TNB and DBK in DMSO yields a brightly colored solution which

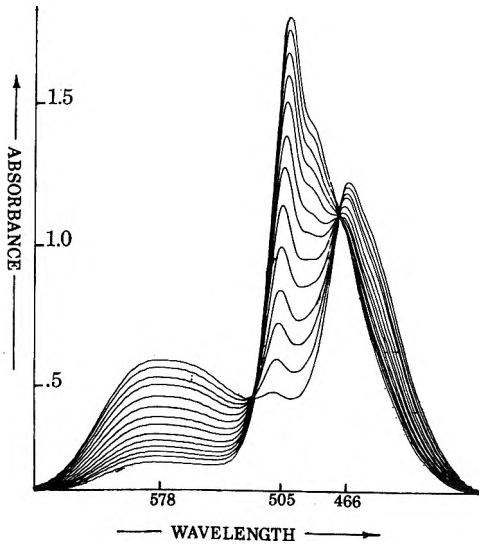


Figure 1.—Visible spectral changes on conversion of 1a to 2. Repeated scans at ~5-min intervals at room temperature.

SCHEME III

Stage I (fast)

$$DBK + NEt_3 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} DBK^- + \overset{+}{H}NEt_3$$

$$DBK^- + TNB \xrightarrow{k_2} \mathbf{1a}$$

Stage II (slow)

$$\mathbf{1a} + NEt_3 \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \mathbf{4} + \overset{+}{H}NEt_3$$

$$\mathbf{4} \xrightarrow{k_4} \mathbf{5}$$

$$\mathbf{5} + \overset{+}{H}NEt_3 \xrightarrow{\text{fast}} \mathbf{2}$$

produces, ultimately, a quantitative yield of the triethylammonium salt of the bicyclic nitropropene nitronate 2. The visible spectral changes which occur show that the reaction takes place in two stages. The first is a rapid formation of a visible spectrum characteristic of the trinitrocyclohexadienate function in **1a**,[1-5] which occurs immediately upon addition of amine to the DMSO solution of TNB and DBK. The rate of this condensation is too fast to follow by conventional means but can be measured by stopped flow spectrophotometric methods. The second stage of the reaction is much slower, and is characterized by the disappearance of absorption due to the σ complex, with concomitant appearance of a spectrum characteristic of the nitropropene nitronate function of 2.[3,14] These spectral changes are illustrated in Figure 1. The structures of the species responsible for the electronic absorption are supported by pmr spectra of the solu-

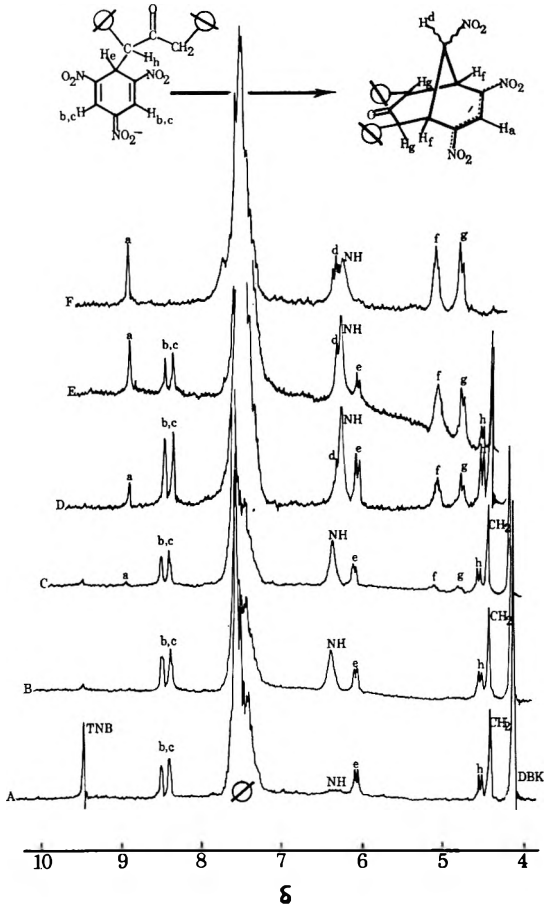
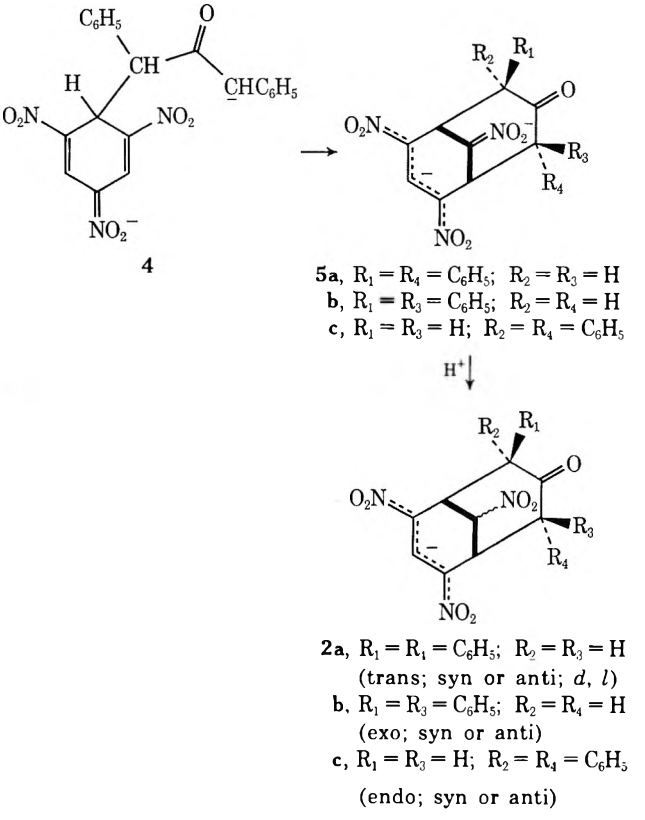


Figure 2.—Nmr spectral changes on conversion of **1a** to **2**: A, 0.11 *M* NEt_3, 0.56 *M* DBK, 0.33 *M* TNB in DMSO-d_6 after 90 sec; B–F, 0.14 *M* NEt_3, 0.17 *M* DBK, 0.11 *M* TNB at ~30-min intervals (B = t_0, spectrum amplitude doubled for D–F).

tions taken over a period of time (Figure 2). The visible spectral changes have been observed with very dilute solutions of reactants and with more concentrated solutions approximating pmr sample concentrations. The latter were obtained with a variable path length quartz cell using path lengths of less than 1 mm. The only species which can be observed in solution by pmr are TNB, DBK, NEt_3, **1a**, and **2b** or **2c**, except at very high concentrations of DBK (*vide infra*). The first three of these have no absorption in the visible region in DMSO solution (separately), whereas **1a** has two maxima at 466 and 578 nm, and **2** has a single maximum at 505 nm. Although **1a** has significant absorption at 575 nm, isolated and purified **2** has none at this wavelength. The rapid appearance and slow disappearance of **1a** could thus easily be followed at 575 nm. Isobestic points are found at 472 and 527 nm.

Although only one 1:1 anionic σ complex, **1a**, can form from TNB and DBK, this complex can cyclize to yield three different bicyclic dianions, **5a**, **5b**, and **5c**. The modes of cyclization of **4**, the dianionic σ complex precursor to **5**, are shown below. Kinetic data substantiating the intermediacy of these dianions is presented in the second section of this paper. In a final rapid step, each of the bicyclic dianions **5** can then be protonated to yield six different singly charged bicyclic products, **2**, since protonation of the unconjugated nitronate moiety in **5** can occur syn or anti to the carbonyl bridge. If the *d* and *l* forms of **2a** are considered, eight isomers are possible. Two of these possible products have been isolated, and there is strong evidence that a third is formed in solution. Before details of the kinetic study are discussed, a presentation of pmr results which clarify these stereochemical problems is pertinent.

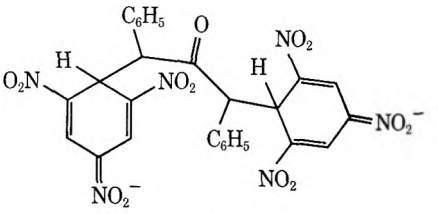


After 90 sec, a solution of 0.11 *M* NEt_3, 0.56 *M* DBK, and 0.33 *M* TNB in DMSO shows a pmr spectrum characteristic of the triethylammonium salt of the σ complex **1a**, a singlet for excess TNB at low field, and absorptions for excess DBK. This spectrum remains unchanged after 2 hr at room temperature. The relative areas of the residual TNB singlet and DBK singlet (methylenes) of ~1:3 confirm that all of the amine has been used in formation of the complex. *Cyclization to bicyclics like* **5** *does not occur in the absence of excess amine.* The pmr spectrum of **1a** (Figure 2, spectrum A) is interesting in several respects because of asymmetry present at the carbon α to the trinitrocyclohexadienate ring. As expected, H_e and H_h are coupled ($J_{e,h}$ ~ 3 cps). The ring protons H_b and H_c of **1a** are magnetically nonequivalent owing to the asymmetry noted, and exhibit different chemical shifts at δ 8.3 and 8.4. They are coupled to each other and to H_e with *J* values less than 1 cps. The shift difference $\Delta_{b,c}$ of ~8 cps between H_b and H_c[22] provides interesting information about the properties of **1a** and its propensity to undergo cyclization in preferred conformations. It has been shown in an earlier report concerned with asymmetry effects on pmr spectra of such complexes[21] that large $\Delta_{b,c}$ values result from large unequal rotamer populations in complexes like **1a**. In addition, the coupling constant $J_{e,h}$ varies widely in a variety of complexes like **1a**[22] (*i.e.*, **1b**, 1 cps; **1c**, 3 cps; **1d**, 5.5 cps). This also

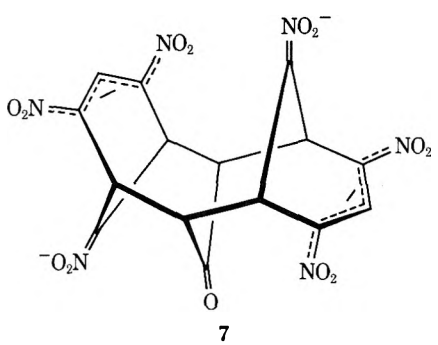
(22) An earlier reported value is 6.5 cps. See M. I. Foreman, R. Foster, and M. J. Strauss, *J. Chem. Soc. B*, 147 (1970).

suggests that such complexes have certain preferred orientations, since vicinal coupling constants depend in large part on the dihedral angle.[23] It is thus not surprising that only certain favored modes of cyclization occur. In a dilute solution of the reactants DBK, TNB, and NEt_3, only one bicyclic product (**2b** or **2c**) is formed. This is shown clearly by changes which occur in the pmr spectrum of the reaction solution with time. In DMSO at concentrations of ~0.14 *M* NEt_3, 0.17 *M* DBK, and 0.11 *M* TNB, rapid formation of **1a** can be observed, followed by its slow disappearance and concurrent formation of **2b** or **2c**. These changes are shown in Figure 2, spectra B–F. Both cis (exo or endo), **2b** or **2c**, and trans, **2a**, bicyclic anions have been prepared as their crystalline triethylammonium salts by methods reported earlier,[11] and their pmr spectra have been discussed. *The spectrum of the cis product* (**2b** *or* **2c**) *is in all respects identical with that which forms in DMSO solution (Figure 2).* No attempt has yet been made to assign stereochemistry at the $CHNO_2$ bridge in **2**. This stereochemistry is determined by a final rapid protonation of **5** in any case (*vide infra*), and its mechanistic features do not affect the magnitude of constants in the rate-limiting expression for formation of **2**. An unambiguous distinction between **2b** and **2c** cannot be made.

Interestingly, in DMSO solutions containing increasing amounts of DBK, cyclization occurs to give more than one of the six possible products. As noted previously, both cis and trans products can be *isolated* as crystalline salts when the reaction is carried out in a neat DBK melt.[11] After 4 hr, pmr spectra of highly concentrated solutions of DBK and TNB in DMSO show evidence of three bicyclic products. Three nitropropene nitronate singlets (H_a, Figure 2) appear between δ 8.1 and 8.7 along with the corresponding sets of peaks upfield. An additional complication at such high concentrations is the appearance (at high spectrum amplitude) of a new set of peaks which probably result from the bis complex **6** at about 1–2% of the intensity of the absorptions of **1a**. The complex **6** is likely analogous to the σ complex precursor of the tetracyclic bisnitronate **7**, described



6



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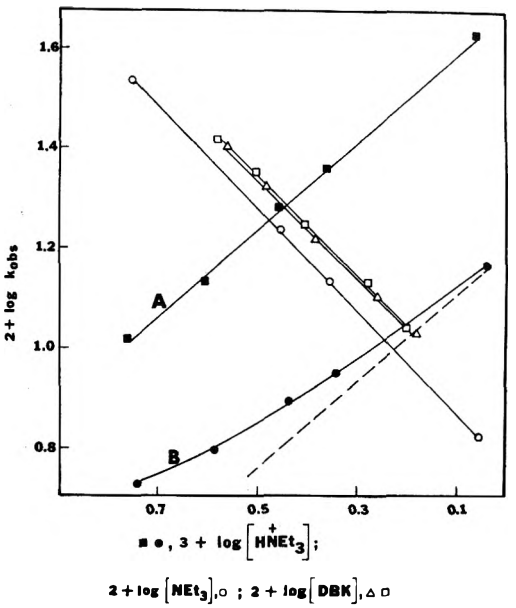


Figure 3.—Effects of NEt_3, $HNEt_3^+$, and DBK on the rate of Stage I.

earlier, which is formed in strongly basic solutions of TNB and acetone.[18] To avoid complicating factors which would make kinetic studies of the formation of **2** very difficult, all reaction rates were measured in very dilute solutions of both TNB and DBK, with the former at 20–100-fold smaller concentration than any other component of the reaction.

State I. Formation of the σ Complex 1a.—Formation of carbanionic σ complexes from ketones and electron-deficient aromatics in the presence of tertiary amines has previously been proposed to occur by the Stage I mechanism shown in Scheme III. No kinetic study has ever been made to support this proposal, probably because no other mode of formation of **1a** seems as plausible. Depending on the relative magnitude of the rate constants involved for the reaction carried out in dilute solution, two types of rate expressions can be expected. If k_{-1} is much larger than k_2 (as well as k_1, so that the carbanion concentration is small relative to that of free ketone), then a preequilibrium expression (eq 1) should be applicable throughout the course of the reaction.

$$+\frac{d[1a]}{dt} = -\frac{d[TNB]}{dt} = k_2K_{eq}\frac{[TNB][NEt_3][DBK]}{[H\overset{+}{N}Et_3]} \quad (1)$$

$$+\frac{d[1a]}{dt} = -\frac{d[TNB]}{dt} = \frac{k_1k_2[DBK][NEt_3][TNB]}{k_{-1}[H\overset{+}{N}Et_3] + k_2[TNB]} \quad (2)$$

If k_2 is of the same order of magnitude as k_{-1}, the steady-state approximation can be applied yielding expression 2. The results of 42 separate runs varying the concentrations of reactants TNB, DBK, NEt_3, and product $HNEt_3^+$ are shown in Table I. Ionic strength was kept constant with $^+NEt_4$, Br^-. Details of the experimental procedure are outlined in the Experimental Section. Generally, a trace of absorbance *vs.* time was generated on the oscilloscope of a Durrum D-110 stopped flow unit by injecting a solution of TNB–DBK and a solution of NEt_3–$HNEt_3^+$–NEt_4^+, both in DMSO, into the reaction chamber. Another identical overlapping trace was generated and the curve was then recorded with an HP oscilloscope

TABLE I

RATE DATA FOR THE STAGE I CONDENSATION IN DMSO AT 25°

Run	Concn, mol/l. TNB × 10^{3}	DBK × 10^{2}	NEt_3 × 10^{2}	$HNEt_3^+$, Br^- × 10^{3}	NEt_4^+, Br^- × 10^{2}	μ × 10	k_{obsd}, sec^{-1}
1	3.228	2.647	2.843	1.151	9.88	1.00	0.422
2	3.228	2.647	2.843	2.301	9.78	1.00	0.228
3 $\Delta HNEt_3^+$, Br^-	3.228	2.647	2.843	2.878	9.74	1.00	0.190
4	3.228	2.647	2.843	4.029	9.59	1.00	0.135
5	3.228	2.647	2.843	5.755	9.42	1.00	0.104
6	3.360	2.773	2.896	1.098		0.0110	0.146
7 $\Delta HNEt_3^+$, Br^- and $\Delta\mu$	3.360	2.773	2.896	2.196		0.220	0.0887
8	3.360	2.773	2.896	2.745		0.0274	0.0779
9	3.360	2.773	2.896	3.843		0.0384	0.0627
10	3.360	2.773	2.896	5.490		0.0549	0.0536
11	3.228	2.647	1.137	2.878	9.71	1.00	0.0740
12 ΔNEt_3	3.228	2.647	2.274	2.878	9.72	1.00	0.151
13	3.228	2.647	2.843	2.878	9.71	1.00	0.191
14	3.228	2.647	5.685	2.878	9.72	1.00	0.384
15	3.360	1.156	3.048	2.766	9.72	1.00	0.119
16	3.360	1.819	3.048	2.766	9.72	1.00	0.141
17 ΔDBK[a]	3.360	2.426	3.048	2.766	9.72	1.00	0.183
18	3.360	3.032	3.048	2.766	9.72	1.00	0.234
19	3.360	3.639	3.048	2.766	9.72	1.00	0.280
20	3.546	1.593	3.172	2.889	9.74	1.00	0.122
21	3.546	1.912	3.172	2.889	9.71	1.00	0.150
22 ΔDBK[b]	3.546	2.549	3.172	2.889	9.70	1.00	0.197
23	3.546	3.186	3.172	2.889	9.70	1.00	0.250
24	3.546	3.823	3.172	2.889	9.71	1.00	0.292
25	3.360	2.773	2.896	2.745	0.997	0.127	0.0962
26	3.360	2.773	2.896	2.745	3.06	0.334	0.127
27 $\Delta\mu$	3.360	2.773	2.896	2.745	4.75	0.503	0.146
28	3.360	2.773	2.896	2.745	6.63	0.691	0.172
29	3.360	2.773	2.896	2.745	8.61	0.889	0.191
30	3.360	2.773	2.896	2.745	10.63	1.09	0.213
31	2.860	2.604	2.401	1.257	0.911	0.1036	0.109
32	2.575	2.604	2.401	1.257	0.911	0.1036	0.110
33 ΔTNB[b]	2.290	2.604	2.401	1.257	0.911	0.1036	0.109
34	2.000	2.604	2.401	1.257	0.911	0.1036	0.112
35	1.715	2.604	2.401	1.257	0.911	0.1036	0.116
36	1.430	2.604	2.401	1.257	0.911	0.1036	0.113
37	2.860	2.510	4.683	1.296	0.911	0.1040	0.239
38	2.290	2.510	4.683	1.296	0.911	0.1040	0.236
39 ΔTNB[a]	1.715	2.510	4.683	1.296	0.911	0.1040	0.241
40	1.145	2.510	4.683	1.296	0.911	0.1040	0.235
41	0.570	2.510	4.683	1.296	0.911	0.1040	0.244
42	0.286	2.510	4.683	1.296	0.911	0.1040	0.242

[a] TNB and DBK in same syringe; NEt_3 and salts in other syringe. [b] DBK, NEt_3, and salts in same syringe; TNB in other syringe.

camera. Solutions of different combinations of reagents were injected, *i.e.*, DBK–NEt_3, to ensure that no preinjection reactions were occurring (*vide infra*). Pseudo-first-order rate constants were obtained assuming that the preequilibrium expression 1 was applicable. Log–log plots of these constants were made against the concentrations of the various reaction components (Figure 3). In all cases, linear relationships were observed with correlation coefficients of 0.999 or greater, which confirms the validity of a mechanism conforming to the preequilibrium expression 1. The slopes of these plots provide the order in each reactant. The individual runs and rate constants are summarized in Table I.

Plots A and B in Figure 3 represent the effects of salt concentration on k_{obsd}. Plot A is constructed from runs 1–5, Table I, and shows the effect of $HNEt_3^+$ concentration at constant ionic strength. The concentration of $HNEt_3^+$ produced as the product geganion of **1a** is at most over 30 times less concentrated than added $HNEt_3^+$, Br^-. The ionic strength was maintained constant with increasing $HNEt_3^+$, Br^- concentration by decreasing the amount of added NEt_4^+, Br^-. The slope of plot A is −0.9. This substantiates the order of −1 predicted by expression 1. In addition, if expression 2 were applicable, a nonlinear log–log plot would be expected. Such a situation is actually observed in the Stage II reaction. Plot B is constructed from runs 6–10 and shows the effect of $HNEt_3^+$, Br^- concentration without added NEt_4^+. At lower $HNEt_3^+$, Br^- concentrations, the slope of this curve approaches −1, but at higher concentrations the increasing ionic strength results in larger rate constants, decreasing the slope, as expected. The overall effect of ionic strength is also as expected for a reaction producing charged species. A plot of log k_{obsd}/k_0 *vs.* $\mu^{1/2}$

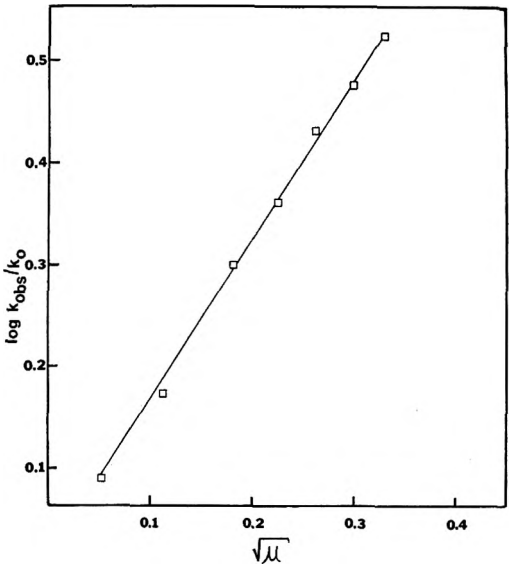


Figure 4.—Effect of ionic strength on Stage I.

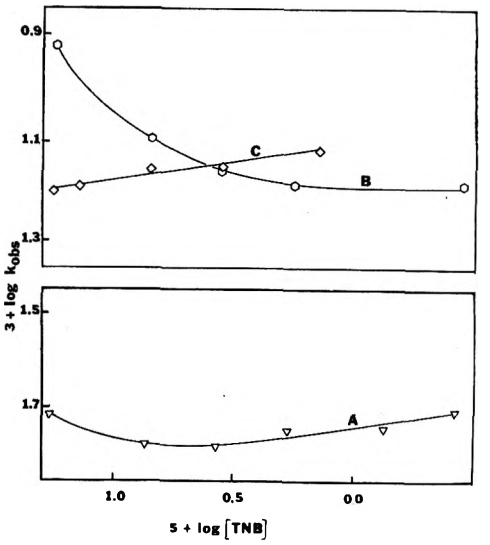


Figure 5.—Effect of TNB concentration on the rate of Stage II: A, runs 49-54; B, runs 43-48; C, runs 55-59.

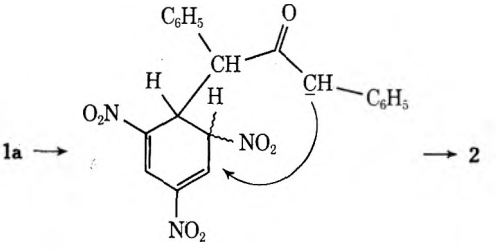
is shown in Figure 4, constructed from runs 25–30, Table I.

The remaining plots shown in Figure 3, runs 11–24, show the effects of NEt_3 and DBK concentration on rate. The slopes are 1.02 and 0.98, respectively. There is no effect observed upon mixing DBK and NEt_3 prior to injection, since the slope remains unchanged from those runs where DBK and TNB were premixed or where DBK and NEt_3 were premixed.

In addition to the above evidence substantiating a preequilibrium mechanism, variation of TNB concentration with all other component concentrations remaining constant did not yield a variation in k_{obsd} as would be expected if a mechanism corresponding to expression 2 were operative (runs 31–42, Table I).

Stage II. Formation of the Bicyclic Anion 2.—We have qualitatively studied cyclizations of a wide variety of σ complexes like **1**, in addition to cyclizations of complexes prepared from 1-carbomethoxy- and 1-cyano-3,5-dinitrobenzenes,[3,13] 1-carbomethoxy- and 1-methyl-2,4,6-trinitrobenzenes,[24] and 1,3-dinitro- and 1,3,6,8-tetranitronaphthalenes.[25] Many of these cyclizations quite probably are mechanistically similar to the cyclization of **1a** to **2**. In order to study this latter cyclization, we used NEt_3 and DBK concentrations approximately 10–100-fold greater than that of TNB. Under these conditions, Stage I was complete within several seconds, even when external triethylammonium bromide was added to the reaction solution. Under similar NEt_3 and $HNEt_3^+$ concentrations, a reaction rate measured in Stage I (run 25, Table I) has a half-life of about 7 sec, whereas the reaction rate measured for Stage II (run 55, Table II) has a half-life of about 50 min. In all the Stage II kinetic runs, Stage I was essentially complete before Stage II began. This point was checked by extrapolating the Stage II runs back to zero time to get the extinction coefficient of **1a** and confirming that all the TNB was converted to complex. This extinction coefficient could be determined from the TNB concentration and absorbance reading at t_∞ (over 8 half-lives) of the Stage I reaction under conditions where Stage II does not occur. The rate of Stage II was followed by measuring the diminishing absorbance of **1a** at 575 nm. The concentrations of DBK, NEt_3, $HNEt_3^+$, and NEt_4^+ were varied and the effect on rate was noted.

Prior to this study we proposed a "least contrived" mechanism in which proton transfer from the exocyclic ketonic moiety to the ring in **1a** was followed by intramolecular attack on the resultant dinitrodiene function of **8**.[3] Such a mechanism circumvented the



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necessity of proposing proton abstraction followed by intramolecular nucleophilic attack on a negatively charged species. This circumvention lead us to an incorrect conclusion, however (*vide infra*). Negative charge on the 2,4,6-trinitrocyclohexadienate function of **1a** resides primarily on the oxygens of the nitro groups (especially that nitro group para to the tetrahedral ring carbon) and the carbocyclic ring may in fact be slightly positive. These conclusions are based on the low field positions of $H_{b,c}$ in the pmr spectrum of **1a** and other similar complexes, as well as on molecular orbital calculations[26] and X-ray crystallographic data,[27] which indicate that structures like **1a** are the major contributors to the ground state of anionic σ complexes. The kinetic data we have generated are consistent with such a picture and show that intramolecular attack does occur in **4** to yield **5**.

Effect of TNB Concentration.—Increasing the TNB concentration in the absence of any externally added

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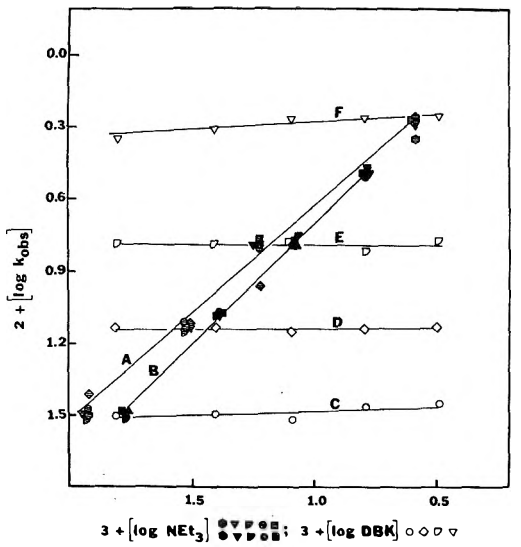

Figure 6.—Effect of NEt_3 and DBK concentrations on the rate of Stage II: A, runs 60–79; B, runs 80–95.

salts results in a dramatic decrease in k_{obsd}, shown in Figure 5, curve B (runs 43–48, Table II). This

TABLE II
EFFECT OF TNB CONCENTRATION ON THE STAGE II CYCLIZATION IN DMSO AT 20°

Run	TNB × 10^4	NEt_3 × 10^2	DBK × 10^2	k_{obsd}, min^{-1}
	Concn, mol/l.			
	Absence of Added Salts			
43	3.516	2.412	2.410	0.0155
44	17.58	2.412	2.410	0.0152
45	35.16	2.412	2.410	0.0143
46	70.32	2.412	2.410	0.0123
47	135.80	2.412	2.410	0.0118
48	175.80	2.412	2.410	0.0101
	Presence of 1.466×10^{-2} *M* NEt_4^+, ClO_4^-			
49	3.678	6.511	6.341	0.0508
50	7.357	6.511	6.341	0.0558
51	18.39	6.511	6.341	0.0562
52	36.79	6.511	6.341	0.0608
53	73.58	6.511	6.341	0.0600
54	183.90	6.511	6.341	0.0515
	Presence of 2.875×10^{-3} *M* $HNEt_3^+$, Br^- and 1.274×10^{-2} *M* NEt_4^+, Br^-			
55	13.98	7.282	6.174	0.0132
56	34.95	7.282	6.174	0.0143
57	69.90	7.282	6.174	0.0142
58	139.80	7.282	6.174	0.0156
59	174.74	7.282	6.174	0.0159

results from the rate-retarding effect on Stage II of increasing $HNEt_3^+$ which is formed in quantitative yield from the Stage I conversion of TNB to the $HNEt_3^+$ salt of **1a**. Superimposed upon this rate depression is a very slight rate increase caused by increasing ionic strength (*vide infra*), and a nonlinear relationship is thus not expected. If the ionic strength is held approximately constant by using a large excess of NEt_4^+, ClO_4^-, and in the presence of a constant excess amount of $HNEt_3^+$, Br^-, this rate depression disappears [Figure 5, line C (runs 55–59, Table II)]. There is in fact a very slight rate increase. The slope of the log–log plot of k_{obsd} *vs.* TNB concentration in this instance is about 0.06. The concentration of TNB thus has no significant effect on the rate of cyclization of **1a** to **2**. At approximately constant ionic strength, but with $HNEt_3^+$ production varying with initial TNB concentration, a rate depression is still observed at high concentrations [Figure 5, curve A (runs 49–54, Table II)].

Effect of NEt_3 and DBK Concentrations.—Log–log plots of NEt_3 concentrations *vs.* k_{obsd} for the Stage II reaction under a variety of different conditions have slopes very close to unity in the presence or absence of added salt (Figure 6, lines A and B). Log–log plots of DBK concentrations *vs.* k_{obsd}, each at differing but constant NEt_3 concentration, have slopes very close to zero in the presence or absence of added salt (Figure 6, lines C–F). These data are summarized in Tables III and IV. It is evident that the cyclization is catalyzed by NEt_3. This rules out a mechanism proceeding through **8**, since NEt_3 would not appear in the rate-limiting expression regardless of how the proton transfers were achieved. Assuming that the Stage II

TABLE III
EFFECTS OF DBK AND NEt_3 CONCENTRATION ON THE STAGE II CYCLIZATION IN DMSO AT 20°

Run	TNB × 10^4	NEt_3 × 10^2	DBK × 10^2	k_{obsd}, min^{-1}
	Concn, mol/l.			
	Presence of 1.820×10^{-4} *M* $HNEt_3^+$, Br^-			
60	0.6939	8.313	0.308	0.0288
61	0.6939	8.313	0.615	0.0301
62	0.6939	8.313	1.230	0.0337
63	0.6939	8.313	2.552	0.0317
64	0.6939	8.313	6.447	0.0320
65	0.6939	3.325	0.308	0.0139
66	0.6939	3.325	0.615	0.0142
67	0.6939	3.325	1.230	0.0147
68	0.6939	3.325	2.552	0.0139
69	0.6939	3.325	6.447	0.0139
70	0.6939	1.663	0.308	0.00626
71	0.6939	1.663	0.615	0.00677
72	0.6939	1.663	1.230	0.00620
73	0.6939	1.663	2.552	0.00643
74	0.6939	1.663	6.447	0.00643
75	0.6939	0.381	0.308	0.00195
76	0.6939	0.381	0.615	0.00196
77	0.6939	0.381	1.230	0.00196
78	0.6939	0.381	2.552	0.00219
79	0.6939	0.381	6.447	0.00245
	Absence of Added Salts			
80	1.358	6.033	6.024	0.0319
81	1.358	6.033	2.410	0.0321
82	1.358	6.033	1.205	0.0323
83	1.358	6.033	0.602	0.0330
84	1.358	2.413	6.024	0.0124
85	1.358	2.413	2.410	0.0128
86	1.358	2.413	1.205	0.0123
87	1.358	2.413	0.602	0.0130
88	1.358	1.207	6.024	0.00652
89	1.358	1.207	2.410	0.00653
90	1.358	1.207	1.205	0.00620
91	1.358	1.207	0.602	0.00604
92	1.358	0.603	6.024	0.00336
93	1.358	0.603	2.410	0.00335
94	1.358	0.603	1.205	0.00331
95	1.358	0.603	0.602	0.00303

TABLE IV
SALT EFFECTS IN THE STAGE II CYCLIZATION IN DMSO AT 20°

Run	TNB × 10⁴	DBK × 10²	NEt_3 × 10²	$HNEt_3^+$, Br^- × 10⁴	NEt_4^+, Br^- × 10²	μ^a × 10	k_{obsd}, min^{-1}
			Concn, mol/l.				
96	0.6840	2.752	4.997	1.773		0.0260	0.02370
97	0.6840	2.752	4.997	3.546		0.0420	0.01710
98	0.6840	2.752	4.997	8.866		0.0950	0.01280
99	0.6840	2.752	4.997	17.732		0.1840	0.00838
100	0.6840	2.752	4.997	35.463		0.3610	0.00480
101	0.6990	6.174	7.282	1.917	1.2740	0.0130	0.04340
102	0.6990	6.174	7.282	3.833	1.2740	0.0130	0.03920
103	0.6990	6.174	7.282	9.583	1.2740	0.0140	0.02850
104	0.6990	6.174	7.282	11.979	1.2740	0.0140	0.01970
105	0.6990	6.174	7.282	28.750	1.2740	0.0160	0.01420
106	0.7358	6.341	2.605		0.0216	0.0030	0.02180
107	0.7358	6.341	2.605		0.0672	0.0075	0.02290
108	0.7358	6.341	2.605		0.3222	0.0329	0.02440
109	0.7358	6.341	2.605		0.7346	0.0742	0.02510
110	0.7358	6.341	2.605		1.5930	0.1600	0.02610

[a] (TNB + salt concentration) since all TNB is converted to triethylammonium salt of σ complex in Stage I.

Intramolecular abstraction of side-chain proton by ring nitronate carbon

$$\mathbf{1a} \underset{}{\overset{K_{eq}}{\rightleftharpoons}} \mathbf{8}$$

$$\mathbf{8} \xrightarrow{k_s} \mathbf{5}$$

$$dP/dt = k_s K_{eq}[\mathbf{1a}] = k_{obsd}[\mathbf{1a}]$$

Intermolecular amine-catalyzed proton transfer from side chain to ring nitronate carbon

$$\mathbf{1a} + NEt_3 \overset{K_{eq}^1}{\rightleftharpoons} \mathbf{4} + \overset{+}{H}NEt_3$$

$$\mathbf{4} + \overset{+}{H}NEt_3 \overset{K_{eq}^2}{\rightleftharpoons} \mathbf{8} + NEt_3$$

$$\mathbf{8} \xrightarrow{k_s} \mathbf{2}$$

$$dP/dt = k_s K_{eq_1} K_{eq_2}[\mathbf{1a}] = k_{obsd}[\mathbf{1a}]$$

sequence outlined in Scheme III is applicable, two rate-limiting expressions can be derived, analogous to the steady-state and preequilibrium treatments of the Stage I formation of **1a**. A distinction between these

$$-\frac{d[\mathbf{1a}]}{dt} = +\frac{d[\mathbf{2}]}{dt} = \frac{k_4 K_{eq}[\mathbf{1a}][NEt_3]}{[\overset{+}{H}NEt_3^+]} \quad (3)$$

$$-\frac{d[\mathbf{1a}]}{dt} = -\frac{d[\mathbf{2}]}{dt} = \frac{k_3 k_4[\mathbf{1a}][NEt_3]}{k_{-3}[\overset{+}{H}NEt_3] + k_4} \quad (4)$$

can be made by examining the effect of $HNEt_3^+$ concentration on the rate.

Effect of Salt Concentration.—Log–log plots of $HNEt_3^+$ and NEt_4^+ concentrations *vs.* k_{obsd} are shown in Figure 7. When $HNEt_3^+$ is constant (equal to initially added TNB) and NEt_4^+ is varied, little effect on the rate is seen (line C). This is expected for a reaction in which charge is neither created nor destroyed. The very slight increase in rate with increasing salt concentration can be attributed to stablilization of increasing charge in the transition state leading to the dianionic intermediate. At constant ionic strength (maintained with an excess of NEt_4^+, Br^-) a log–log plot, B, of $HNEt_3^+$ *vs.* k_{obsd} is nonlinear with an approximated slope of about −0.4, consistent with eq 4 and not eq 3. A similar nonlinear curve is generated from an identical plot, A, in which the ionic

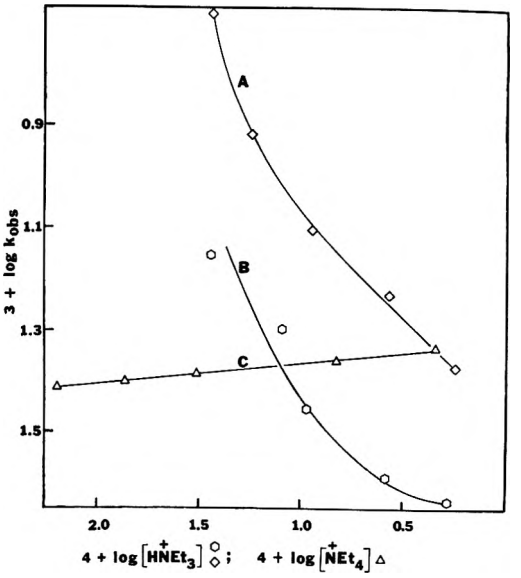

Figure 7.—Effect of $HNEt_3^+$ and NEt_4^+ concentrations on the rate of stage II: A, runs 96–100; B, runs 101–105; C, runs 106–110.

strength was not kept constant. This differs little from B, except that the reaction is much slower at all $HNEt_3^+$ concentrations.

General Conclusions.—The short-lived intermediates **4** and **5** are quite reasonable structures, and are supported by the stable and isolable compound **7** and the characterization of bis-sulfite complexes of TNB.[19,28] In fact, we have found that **2** can be converted back to **5** in strong base. Addition of excess triethylamine to a solution of **2** (cis) in DMSO followed by aging this solution for several weeks causes broadening and loss of resolution of the $CHNO_2$ triplet in **2**, which strongly indicates nitronate formation at this bridge. Such changes occur more rapidly upon addition of NaOH. In addition, other changes in the pmr spectra of solutions of the cis or trans isomer occur. After a period of weeks in the presence of excess triethylamine, a partial decrease of resonances of cis adduct occurs concurrently with appearance of resonances attributable

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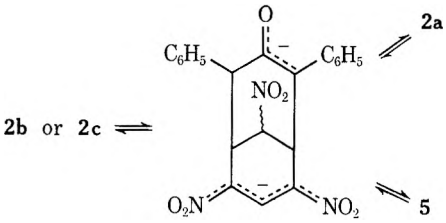
to the trans isomer **2a**. This isomerization undoubtedly proceeds through the enolate of **2**, followed by reprotonation. The trans isomer **2a** is thus likely to be more thermodynamically stable than the cis. It is difficult to assess the detailed changes which are occurring owing to the complexity of the spectra which are generated upon aging a solution of **2** in base. No reversion to **1a** occurs, however, since the visible maximum of the aging solutions remains at 505 nm, showing no reappearance of absorption characteristic of **1a**.



Studies of cyclization mechanisms of carbanionic σ complexes to yield structures like **2** have been carried out in other laboratories.[19,20,29,30] Although the isolated crystalline bicyclic products have been correctly characterized in most of these studies, the specious mechanistic schemes proposed are for the most part conjecture, based on qualitative shifts in the uv–visible absorption maxima of reactant solutions. Such evidence is tenuous at best.[29,30]

Experimental Section[31]

Purification of Reagents.—Dimethyl sulfoxide (Mallinckrodt analytical reagent) was distilled from calcium hydride under vacuum on a spinning band column. It was stored under dry nitrogen until used. The specific conductance of DMSO purified in this fashion was less than 3×10^{-8} ohm^{-1} cm^{-1}, which is in excellent agreement with conductance values obtained for DMSO containing less than 4 ppm water.[32] Triethylamine (Baker) was distilled from small quantities of phenyl isocyanate.[33] The distillate was then redistilled from molecular sieves (4A) and the amine was collected at 89°. Only a single sharp peak was observed on chromatographic analysis using an HP-700 vpc (4 ft × 0.25 in. column, 30% Citroflex on Chromosorb W 60–80 mesh) at 65°. Dibenzyl ketone (Eastman) was recrystallized from pentane and dried under vacuum at room temperature for at least 8 hr. The crystals were then recrystallized from dry pentane, dried, and stored over P_2O_5 under nitrogen in a cold box to prevent melting (mp 34°, lit.[34] mp 35°). Triethylammonium bromide (Eastman) was recrystallized from anhydrous ethanol and dried at 110° (3 mm) for at least 8 hr. Tetraethylammonium bromide was recrystallized from a mixture of chloroform and benzene. The recrystallized salt was dried at 110° (3 mm) for at least 8 hr. Both the tri- and tetraethylammonium salts were stored in a drybox over P_2O_5. Tetraethylammonium perchlorate was purified as described previously.[35] Trinitrobenzene was repeatedly recrystallized from ethanol–water solutions which were decolorized with activated carbon. After three recrystallizations, colorless plates, mp 123° (lit.[36] mp 123°), were obtained. These were stored in a drybox at 0° until needed. In an alternate method of purification, TNB was sublimed at reduced pressure.[36] Crystals melting at 123° were obtained by this method.

Stage I Kinetic Runs.—Stock solutions of TNB, NEt_3, DBK, and the salts were prepared in DMSO and the required quantities for each run were pipetted into volumetric flasks and diluted to volume. Except where noted, the TNB and DBK were in one flask and NEt_3 and the salts were in another flask. Because of the low solubility of NEt_4^+, Br^- in DMSO, the required quantities of this salt were weighed separately for each run. In addition, because this salt is extremely hygroscopic, all weighings were done on an analytical balance in a dry bag under a dry nitrogen atmosphere.

After injection of the appropriate solutions into the reaction chamber of the spectrophotometer thermostated at 25°, the trace of absorbance at 575 nm *vs.* time recorded on the oscilloscope was copied with a Hewlett-Packard oscilloscope camera (Model 198-A). Two identical traces were recorded before a picture was taken. Absorbance and time values were taken from the curves with a circular film measuring device and were used for computation of pseudo-first-order rate constants in the region of 20–60% completion. Rate constants were obtained from the slopes of plots of ln $(A_\infty - A_t)$ *vs.* time. These plots were generated from a "LORDHELPUS" program[37] using a Xerox Sigma 6 computer. The program was designed specifically for analysis of a large amount of data, allowing job submittal from cards or terminal. It yields the rate constant and ln A_0 value (where A_0 is the absorbance at $t = 0$) from a series of absorbance and corresponding time values of a particular run. Runs with either increasing or decreasing absorbance as a function of time may be evaluated.

Stage II Kinetic Runs.—The Stage II kinetics were determined by mixing the appropriate solutions (preequilibrated to 20°) and transferring the reaction mixture to a thermostated cuvette in a Cary 14 spectrophotometer. The decrease in absorbance as a function of time was then recorded. The data were analyzed from the plot of absorbance *vs.* time as described for Stage I.

Acknowledgments.—The authors wish to thank the Army Research Office at Durham and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Registry No.—**1a**, 26986-18-5; **2**, 12379-64-5; DBK, 102-04-5; TNB, 99-35-4.

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Reactions of Methylcalcium Iodide

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Received April 24, 1973

Methylcalcium iodide was shown to be a useful organometallic reagent in several fundamental organic reactions in tetrahydrofuran. Reactions at −30° with benzaldehyde, acetone, benzophenone, methyl acetate, and diethyl carbonate gave the corresponding addition products in good yields. In the reaction with methyl crotonate, the carbonyl addition much predominated over the 1,4 addition. Both the coupling and the addition reactions were observed in the reactions with acid halides. The reagent gave the corresponding ketones in low yields by the reaction with nitriles, reacted but slowly with benzyl chloride and 1,1-diphenylethylene, and did not react with cyclohexene.

The development of organocalcium chemistry has been very slow when compared with that of other organometallic areas. The slow progress could have been due to the lack of a simple method to prepare organocalcium compounds. In a previous paper,[1] we demonstrated that the reaction of organic halides with calcium metal in tetrahydrofuran gave the corresponding organocalcium halides in much better yields than those available in the literature, and the range of suitable halides was extended (eq 1). The

$$RX + Ca \longrightarrow RCaX \quad (1)$$

key ingredient appeared to be the availability of higher purity calcium metal than was previously obtainable. In the present study, we aimed to elucidate the property of methylcalcium iodide in several fundamental organic reactions in tetrahydrofuran.

Although reactions of organocalcium iodides have been studied,[2-20] the available data in the literature are limited. An important problem that troubled the previous authors was the low yield of organocalcium halides. Nevertheless, reactions of arylcalcium iodides were relatively well investigated. Reaction of phenylcalcium iodide with benzophenone anil gave triphenylmethylaniline in 78% yield;[4] with benzoyl chloride, ethyl benzoate and benzophenone gave triphenylmethanol in 94, 80, and 80% yields, respectively;[7] that with α-bromonaphthalene gave after carboxylation α-naphthoic acid in 98% yield;[7] that with pyridine gave a mixture of mono- and diphenylated pyridine.[7] Metalation of fluorene, indene, triphenylmethane, pentafluorobenzene and thiophene by phenylcalcium iodide gave the expected products in 10–53% yields.[10,16] Examples of the addition of arylcalcium iodides to vinylacetylenes have been reported.[9,11,12,14,15] Yields of products were low or were not given in the reactions of arylcalcium iodides with benzaldehyde,[2] phenyl isocyanate,[3] benzonitrile,[4] dibenzofuran,[4] dibenzothiophene,[5] and anisol.[7]

On the other hand, only a very few data are available in the literature on the reaction of aliphatic organocalcium halides. Moreover, yields of products were generally low in these cases. Contrary to the case of arylcalcium iodides,[7,10,16] carboxylation of alkylcalcium iodides did not quantitatively give the corresponding carboxylic acids.[6,7] The reaction of methylcalcium iodide with benzaldehyde gave α-methylbenzyl alcohol in only 10% yield;[7,17] reaction with thiophene gave after carboxylation thiophene-2-carboxylic acid in 21% yield.[7] Bogatskii and coworkers[8] reported that methylcalcium iodide promoted the aldol condensation of acetone and other carbonyl compounds, and that it did not undergo the addition reactions to these carbonyl compounds. Chastrette and Gauthier[18] reported that a solution of methylcalcium iodide in tetrahydrofuran underwent only addition to diisopropyl ketone to give α,α-diisopropylethanol, while the solid methylcalcium iodide underwent only reduction of the ketone. Cherkasov and coworkers[9,11-15,19,20] reported examples of the addition of alkylcalcium iodides to vinylacetylenes. Metalation of carbon acids by alkylcalcium iodides was reported to result in low yields of the expected products.[10]

Judging from these limited results reported by previous authors, organocalcium halides seem to resemble organolithium reagents and should be useful in organic syntheses. However, available data in the literature are limited and yields of products by previous authors were generally low especially in the aliphatic series. If the limitation is due to difficulties in the preparation of organocalcium halides, and their low yields are derived from some impurities contained in the calcium metal and/or the organocalcium reagents, organocalcium halides might yet be useful in organic syntheses if these factors could be overcome. These difficulties have been overcome,[1]

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(18) M. Chastrette and R. Gauthier, *C. R. Acad. Sci., Ser. C*, **274**, 2013 (1972).
(19) L. N. Cherkasov, *Zh. Obshch. Khim.*, **42**, 1528 (1972).
(20) L. N. Cherkasov, *Zh. Vses. Khim. Obshchest.*, **17**, 111 (1972); *Chem. Abstr.*, **76**, 99010g (1972).

and in this paper we examined the utility of methylcalcium iodide in several fundamental organic reactions.

Results and Discussion

We prepared methylcalcium iodide in tetrahydrofuran according to the procedure reported previously.[1] Owing to the poor solubility in tetrahydrofuran, the methylcalcium iodide was obtained as a suspension. The suspension was used for further reactions without the isolation of the methylcalcium iodide. We added a tetrahydrofuran solution of various reactants to this suspension at −30°. Yields of products were, therefore, calculated based on the amount of methyl iodide used in the preparation of methylcalcium iodide. We also estimated the yields of products based on methylcalcium iodide and gave these in parenthesis in the text. This estimation was based on the result that the yield of methylcalcium iodide in tetrahydrofuran was generally 91–93% based on methyl iodide.[1]

We used calcium metal of higher purity than was available before. This made several improvements upon the experimental procedure of the reaction of organocalcium halides. Bryce-Smith and Skinner[7] as well as Chastrette and Gauthier[18,21] activated calcium by amalgamation, and Cherkasov and coworkers[9,11–15,19,20] activated calcium by heating with magnesium and mercury. Therefore, there would be some organomercury or organomagnesium compounds mixed in their organocalcium iodides, and their experimental results could be influenced by the presence of these impure organometallic compounds. Since the activation was not necessary when calcium metal of higher purity was used, the effect of such impure organometallics would be minimized.

The yields of alkylcalcium iodides by previous workers were generally very low, and a considerable amount of calcium iodide produced by the Wurtz-type coupling, the most important side-reaction of reaction 1, was present. The presence of such a by-product might exert some influence upon the organic reactions of alkylcalcium iodides, since the presence of lithium halides was reported to exert a large influence upon the reaction of lithium carbenoids,[22] and the presence of magnesium halides was also reported to produce a remarkable effect on the reactions of organozinc[23,24] and organocadmium compounds.[25,26] We obtained methylcalcium iodide 91–93% yield using the higher purity calcium metal, and the influence of calcium iodide would be minimized.

Reaction of methylcalcium iodide with acetone gave *tert*-butyl alcohol in 49–51% (53–56%) yield. We also observed the formation of methane in 37–39% (40–43%) yield during the reaction. The result is in a striking contrast to that reported recently by Bogatskii and coworkers.[8] They observed only the aldol condensation of acetone to diacetone alcohol. We feel some doubt on the purity of their methylcalcium iodide. Calcium metal and methylcalcium iodide are sensitive to atmospheric oxygen and moisture. When the calcium metal and/or methylcalcium iodide were improperly treated, oxide and hydroxide of calcium would be introduced to the reaction system. These compounds are strong inorganic bases and would facilitate the aldol condensation, but would not give *tert*-butyl alcohol by the reaction with acetone.

Reaction of methylcalcium iodide with an excess of benzophenone gave α,α-diphenylethanol in 76% (82–84%) yield. When a nearly equimolar amount of benzophenone was used, the yield of α,α-diphenylethanol was lower, and a part of methylcalcium iodide remained unchanged in the reaction system. The result was due to the fact that we used an excess of calcium metal in the preparation of methylcalcium iodide. The reaction of metallic calcium with benzophenone to form benzophenone calcium ketyl seemed to be much faster than the addition reaction of methylcalcium iodide with benzophenone.

Reaction of methylcalcium iodide with benzaldehyde gave α-methylbenzyl alcohol in 55–64% (59–70%) yield. Meanwhile Bryce-Smith and Skinner[7] as well as Bogatskii and coworkers[17] obtained the alcohol only in 10% yield by the same reaction in tetrahydrofuran at −50°. The discrepancy could be ascribable to the difference in the purity of methylcalcium iodide.

The reaction of methylcalcium iodide with methyl acetate gave *tert*-butyl alcohol in 70–71% (75–78%) yield. During the reaction, we observed the formation of methane in 17–21% (18–23%) yield. The reaction with diethyl carbonate gave *tert*-butyl alcohol and acetone in 68–73% (73–80%) and 3–6% (3–7%) yields, respectively. The reaction with an α,β-unsaturated ester, methyl crotonate, gave the carbonyl adducts, 2-methyl-3-penten-2-ol and ethylideneacetone, in 50% (54–55%) and 4% (4%) yields, respectively, together with a small amount of methyl isovalerate. During the reaction, we observed the formation of methane in 17% (18–19%) yield. Thus the carbonyl addition predominated over the 1,4 addition. This result forms a marked difference with the case of the reaction of calcium zinc tetrabutyl with α,β-unsaturated ketones. The latter reaction was reported to show 1,4 addition and hydrogen abstraction without carbonyl addition.[27]

We observed both coupling and addition reactions between methylcalcium iodide and acid chlorides. The reaction of methylcalcium iodide with benzoyl chloride gave α-methylstyrene in 70% (75–77%) yield, together with a small amount of acetophenone and α,α-dimethylbenzyl alcohol. The reaction of methylcalcium iodide with acetyl chloride gave *tert*-butyl alcohol and *tert*-butyl acetate in 22–31% (24–34%) and 19–26% (20–29%) yields, respectively, together with a small amount of acetone. During the reaction, we observed the formation of methane in 25–26% (27–29%) yield.

Reaction of methylcalcium iodide with acetonitrile gave acetone only in 9–14% (10–15%) yield, and methane formed in 60% (64–66%) yield during the reaction. The hydrogen abstraction reaction predominated over

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(24) B. Marx, *C. R. Acad. Sci., Ser. C*, **266**, 1646 (1968).
(25) J. Kollonitsch, *Nature (London)*, **188**, 140 (1960).
(26) J. Kollonitsch, *J. Chem. Soc., A*, 453, 456 (1966).
(27) Y. Kawakami, Y. Yasuda, and T. Tsuruta, *Bull. Chem. Soc. Jap.*, **44**, 1164 (1971).

TABLE I

REACTIONS OF METHYLCALCIUM IODIDE WITH VARIOUS COMPOUNDS IN TETRAHYDROFURAN[a]

Registry no.	Compd	Mmol	Ca, mmol	CH_3I, mmol	THF,[b] ml	Products (yield, %[c])
67-64-1	CH_3COCH_3	5.1	7.1	5.0	12	$(CH_3)_3COH$ (49), CH_4 (39)
	CH_3COCH_3	4.9	5.9	4.5	10	$(CH_3)_3COH$ (51), CH_4 (37)
119-61-9	$C_6H_5COC_6H_5$[d]	6.2	8.5	5.7	15	$CH_3C(C_6H_5)_2OH$ (32)
	$C_6H_5COC_6H_5$	16.8	9.1	5.9	17	$CH_3C(C_6H_5)_2OH$ (76)
100-52-7	C_6H_5CHO	6.6	7.9	5.9	15	$C_6H_5CH(CH_3)OH$ (64), $C_6H_5CH{=}CH_2$ (trace)
	C_6H_5CHO	12.0	9.2	6.2	15	$C_6H_5CH(CH_3)OH$ (55), $C_6H_5CH{=}CH_2$ (trace)
79-20-9	CH_3COOCH_3	3.4	7.7	6.0	14	$(CH_3)_3COH$ (71), CH_4 (21)
	CH_3COOCH_3	3.3	7.5	6.0	14	$(CH_3)_3COH$ (70), CH_4 (17)
105-58-8	$(C_2H_5O)_2CO$	1.8	7.1	5.1	12	$(CH_3)_3COH$ (68), CH_3COCH_3 (3)
	$(C_2H_5O)_2CO$	2.2	8.0	6.0	14	$(CH_3)_3COH$ (73), CH_3COCH_3 (6)
18707-60-3	$CH_3CH{=}CHCOOCH_3$	6.6	9.4	6.0	15	$CH_3CH{=}CHC(CH_3)_2OH$ (50), $CH_3CH{=}CHCOCH_3$ (4), $(CH_3)_2CHCH_2COOCH_3$ (trace), CH_4 (17)
98-88-4	C_6H_5COCl	6.0	8.0	5.8	15	$CH_2{=}C(CH_3)C_6H_5$ (70), $C_6H_5COCH_3$ (trace), $C_6H_5C(CH_3)_2OH$ (trace)
75-36-6	CH_3COCl	3.4	8.1	6.0	14.5	$(CH_3)_3COH$ (31), $CH_3COOC(CH_3)_3$ (19), CH_3COCH_3 (trace), CH_4 (25)
	CH_3COCl	6.2	7.4	5.9	14	$(CH_3)_3COH$ (22), $CH_3COOC(CH_3)_3$ (26), CH_3COCH_3 (2), CH_4 (26)
75-05-8	CH_3CN	6.5	8.5	5.9	14	CH_3COCH_3 (14), CH_4 (60)
	CH_3CN	6.2	9.6	6.0	14	CH_3COCH_3 (9), CH_4 (60)
100-47-0	C_6H_5CN	6.1	8.6	6.0	15	$C_6H_5COCH_3$ (18)
	C_6H_5CN	6.6	7.6	5.9	15	$C_6H_5COCH_3$ (21)
	C_6H_5CN	6.6	8.6	5.9	15	$C_6H_5COCH_3$ (21)

[a] Reactions were carried out at −30° under a nitrogen atmosphere. [b] Tetrahydrofuran. [c] Based on CH_3I. [d] 27% of methylcalcium iodide remained unchanged.

the addition reaction. The reaction with benzonitrile gave acetophenone in 18–21% (19–23%) yield. Distillation of the reaction products left a viscous undistillable residue, apparently polymeric.

The reaction of methylcalcium iodide with olefins appeared to be very slow. The calcium compound did not react with cyclohexene in tetrahydrofuran even at 20° for 60 hr. According to the descriptions in the literature, however, organocalcium iodides undergo addition reactions with vinylacetylenes,[9,11-15,19,20] and alkylcalcium iodides can initiate polymerization of conjugated dienes in the presence of hexamethylphosphoramide,[28,29] and copolymerization of styrene and butadiene.[30] Thus, organocalcium halides seem to react with conjugated olefins to some extent. However, we found that methylcalcium iodide was poorly reactive toward 1,1-diphenylethylene in tetrahydrofuran. When 1,1-diphenylethylene was added to the suspension of methylcalcium iodide in tetrahydrofuran, a dark red color developed but the yield of 1,1-diphenylpropane was negligible even after 60 hr at 20°.

The rapid reaction of organolithium compounds with benzyl chloride is the basis for a quantitative analysis of organolithium compounds by double titration.[31] On the other hand, the procedure was reported to give unpromising results with organocalcium halides.[7] We observed that the reaction of methylcalcium iodide with benzyl chloride was slow. When the reaction was carried out for 1 hr at 20°, ethylbenzene was obtained only in 6% (6–7%) yield, and 46% (49–51%) of methylcalcium iodide remained unchanged in the reaction system. The yield of ethylbenzene was only 13% (14%) even after 17 hr at 20°.

When one attempts to carry out the reaction of organocalcium halides in ethereal media, particular attention should be given to the reaction of the reagents with the solvent. Although tetrahydrofuran and other ethereal solvents are convenient media for the preparation of organocalcium halides, they are readily cleaved by organocalcium reagents. Bryce-Smith and Skinner[7] described that the half-life of methylcalcium iodide in tetrahydrofuran at 20° was 13 days. However, we observed that methylcalcium iodide was much less stable. The half-life in tetrahydrofuran at 20° was ~10 hr. Although the calcium compound was somewhat more stable at lower temperature, it was necessary to use the reagent for further reactions immediately after the preparation. The cleavage reaction is significant in the slow reactions of the organocalcium reagents, *e.g.*, reactions of methylcalcium iodide with benzyl chloride and olefins.

Results are summarized in Table I.

Judging from the above results, we can confirm the similarity[7] of organocalcium halides with organolithium reagents in several fundamental organic reactions. Methylcalcium iodide undergoes addition reactions with various carbonyl compounds to give the expected products in good yields. In the reaction with an α,β-unsaturated ester, the carbonyl addition much predominated over the 1,4 addition. Thus, organocalcium halides would be useful in organic syntheses, although methylcalcium iodide gave the corresponding ketones in

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(29) N. A. Smirnyagina and E. I. Tinyakova, *Dokl. Akad. Nauk SSSR*, **186**, 1099 (1969).

(30) N. A. Smirnyagina and E. I. Tinyakova, *Dokl. Akad. Nauk SSSR*, **192**, 109 (1970).

(31) H. Gilman and A. H. Haubein, *J. Amer. Chem. Soc.*, **66**, 1515 (1944).

low yields by the reaction with nitriles, and reacted very slowly with olefins. The characteristic nature of organocalcium halides in organic reactions remains to be revealed in the future.

Experimental Section

Gas chromatographic analyses were carried out on a Shimadzu GC-4A or GC-4B gas chromatograph. Infrared spectra were recorded on a Japan Spectroscopic Co. Model 402G spectrometer.

Materials.—Methylcalcium iodide was prepared in tetrahydrofuran according to our procedure reported previously.[1] Tetrahydrofuran was purified by distillation in the presence of benzophenone sodium ketyl under a nitrogen atmosphere. Nitrogen was purified by passing through a tube containing copper turnings in a furnace at 170° followed by drying with phosphorus pentoxide. Methyl iodide, acetone, benzophenone, benzaldehyde, benzoyl chloride, acetyl chloride, methyl acetate, diethyl carbonate, methyl crotonate, acetonitrile, benzonitrile, benzyl chloride, cyclohexene, and 1,1-diphenylethylene were purified by usual methods.[32] Authentic samples of 2-methyl-3-penten-2-ol and α,α-diphenylethanol were prepared by the reactions of methylmagnesium iodide with *n*-butyl crotonate and benzophenone, respectively. 1,1-Diphenylpropane was prepared by a conventional procedure.[33,34] Other authentic samples and chemicals were commercial products and were used without further purification.

Procedure.—The reaction vessel was a two-necked flask equipped with two three-way cocks. Each three-way cock was connected with a nitrogen inlet and a rubber serum cap. Methylcalcium iodide was prepared in this flask by the reaction of calcium metal with methyl iodide in tetrahydrofuran at −70°.[1] Various reactants in tetrahydrofuran were added dropwise at −30° to this methylcalcium iodide in the flask over a period of 0.5 hr while stirring at the temperature. Reactons with carbonyl compounds and nitriles were rapid and exothermic, and the stirring was continued for 1 hr at 20° to complete the reaction. Reactions with benzyl chloride, cyclohexene, and 1,1-diphenylethylene were slow and were continued for several hr at 20° after the addition of the reactants. After the reaction, water, methanol, acetic acid, or 6 *N* hydrochloric acid was added to the reaction mixture. The amount of gaseous products evolved during the reaction was determined by a gas burette, and the gas was analyzed by gas chromatography. Qualitative and quantitative analyses of other reaction products were carried out by gas chromatography.

Registry No.—Methylcalcium iodide, 20458-43-9.

(32) J. A. Riddick and W. B. Bunger, "Organic Solvents," 3rd ed, Wiley-Interscience, New York, N. Y., 1970.

(33) C. F. H. Allen and S. Converse, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1932, p 226.

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Inversion of Configuration in the Bromination of Vinylic Mercurials[1]

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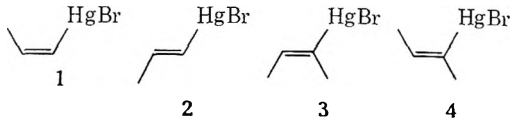
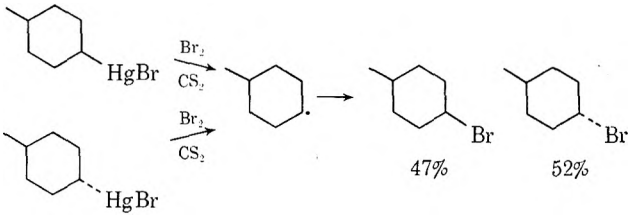
Received March 28, 1973

The bromination of *cis*- and *trans*-1-propenyl- and 2-butenylmercury(II) bromide in carbon disulfide occurs with predominant inversion of configuration at the double bond. The rate of bromination of *trans*-2-butenylmercury(II) bromide in carbon disulfide is 75 times as fast as that of *n*-propylmercury(II) bromide. The observed inversion of configuration is consistent with a trans addition of bromine to the carbon–carbon double bond of the vinylic mercurials followed by a trans elimination of mercury(II) bromide. In contrast to the results in carbon disulfide, the bromination of the vinylic mercurials takes place with retention of configuration in pyridine.

A study of the bromination of *cis*- and *trans*-2-butenyl- and 1-propenylmercury(II) bromides (compounds **1**, **2**, **3**, and **4**) in carbon disulfide was initiated in an attempt to generate free propenyl radicals of known stereochemistry and to investigate their stereochemical fate.[2] A free-radical pathway for the bromination of these compounds in carbon disulfide was



anticipated at the outset, since Jensen had shown that the bromination of either *cis*- or *trans*-4-methylcyclohexylmercury(II) bromide in degassed carbon disulfide produced the same ratio of *cis*- and *trans*-1-bromo-4-methylcyclohexane and had interpreted the loss of of stereochemistry in terms of a free-radical reaction.[3] The possibility of an alternative pathway involving retention of stereochemistry in the bromination of the



vinylic mercurials was also considered, since Jensen[3] had shown that the bromination of the isomeric methylcyclohexyl mercurials in methanol proceeds with 85% retention of stereochemistry. Here, we report the surprising finding that bromination of 1-propenyl and 2-butenyl mercurials leads to propenyl and butenyl bromides of inverted stereochemistry.[4]

Results

Synthesis and Stereochemistry of Vinylic Mercurials.—*cis*- and *trans*-1-propenyl- and 2-butenylmercury(II)

(1) Supported in part by the National Science Foundation, Grants GP-28586X and GP-2018.

(2) L. A. Singer in "Selective Organic Transformations," Vol. II, B. S. Thyagarajan, Ed., Wiley, New York, N. Y., 1972, p 239.

(3) F. R. Jensen and L. H. Gale, *J. Amer. Chem. Soc.*, **82**, 148 (1960).

(4) Although the chemistry of *cis*- and *trans*-1-propenylmercury(II) bromides has been studied in detail,[5] the halogenation of these compounds has not been reported.

(5) A. N. Nesmeyanov, A. E. Borisov, and N. V. Novikova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1216 (1959); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1174 (1959).

TABLE I
BROMINATION OF VINYLIC MERCURIALS IN PYRIDINE AND CARBON DISULFIDE

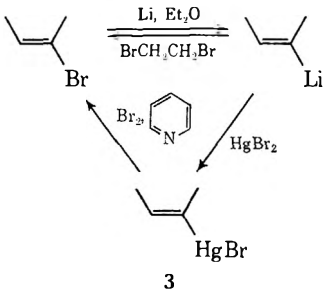
Compd	Conditions	RHgBr, mmol	Br_2, mmol	Vinyl bromides, Cis:trans		Yield, %
Cis, **3**	Pyridine, air, 0.035 *M*	0.25	0.25	99.6	0.4	92
Trans, **4**	Pyridine, air, 0.035 *M*	0.25	0.25	8.9	91.9	95
Cis, **1**	CS_2, air, 0.05 *M*	0.11	0.11	21.8	78.2	
Trans, **2**	CS_2, air, 0.05 *M*	0.10	0.10	73.5	26.5	
Cis, **3**	CS_2, air, 0.03 *M*	0.27	0.27	11.6	88.4	100
Trans, **4**	CS_2, air, 0.06 *M*	0.20	0.20	92.9	7.1	102
Trans, **4**	CS_2, degassed, 0.06 *M*	0.12	0.12	91.8	8.2	
Trans, **4**	MeOH, air, 0.02 *M*	0.02	0.02	77.8	22.2	

bromide were synthesized stereospecifically by reaction of mercury(II) bromide with the corresponding vinylic lithium reagents[6] prepared from stereochemically pure vinylic bromides. The isomeric 1-propenyl- and 2-butenyllithium reagents had been prepared previously and demonstrated to be configurationally stable, once formed.[7-9] The stereochemistry of *cis*- and *trans*-1-propenylmercury(II) bromide, **1** and **2**, was originally assigned by Nesmeyanov[5] on the basis of the method of synthesis from the corresponding lithium reagents. Jensen[10] has recently demonstrated that *exo*- and *endo*-2-norbornylmagnesium bromide react with mercury(II) bromide to give the corresponding alkylmercury(II) bromides with complete retention of configuration. The stereochemistry of di-*cis*- and di-*trans*-propenylmercury(II), **5** and **6**, respectively, has been assigned unambiguously by nmr.[11]

The assignment of stereochemistry of *cis*- and *trans*-2-butenylmercury(II) bromide is based on the method of synthesis and on the nmr spectra of the compounds. Owing to deshielding by the cis mercury atom,[11] the chemical shift of the vinyl proton cis to mercury in **3** is δ 5.56 while the chemical shift of the vinyl proton trans to mercury in **4** is δ 6.25.

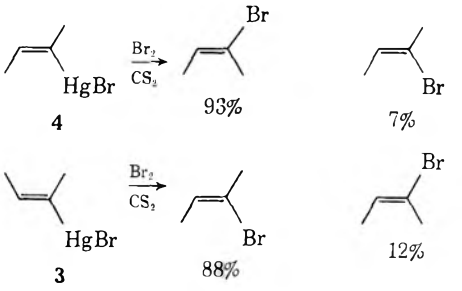
The reaction of alkyl mercurials with bromine in pyridine is stereospecific.[3] We have found that the reaction of the vinylic mercurials **3** and **4** with bromine in pyridine produces the corresponding vinylic bromides with retention of configuration (Table I). The chemical evidence for the assignment of configuration of *cis*-2-butenylmercury(II) bromide, **3**, is shown in Scheme I.

SCHEME I



3

Bromination of Vinylic Mercurials in Carbon Disulfide.—The bromination of the vinylic mercurials **1**, **2**, **3**, and **4** in carbon disulfide was highly stereoselective but gave vinyl bromides having opposite stereochemistry from the mercury compounds from which they were derived (Table I). Similar results were obtained in degassed solutions or in the presence of air, which normally retards free-radical bromination of mercurials.[3] Bromination of **4** in methanol also gave predominantly the vinylic bromide of opposite configuration.



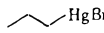
Relative Rates of Bromination of Alkyl and Vinylic Mercurials.—To aid in the determination of the mechanism of the bromination of the vinylic mercurials, it was of interest to determine the relative rates of bromination of 1-hexene, *trans*-2-butenylmercury(II) bromide, **4**, and *n*-propylmercury(II) bromide. Since both vinylic and alkylmercury(II) compounds decolorize carbon disulfide or pyridine solutions of bromine immediately, competition techniques were used to measure relative rates. Dilute carbon disulfide or pyridine solutions of pairs of the substrates were treated with a deficiency of a dilute solution of bromine. The relative yields of the two products were determined by gas chromatography and used to establish the relative rates of bromination shown in Table II.

Discussion

Two mechanisms for the halogenation of organomercurials have been demonstrated.[12] In polar solvents in the presence of air (a free-radical inhibitor), haolgenation of alkylmercury(II) halides proceeds by a stereospecific four-center mechanism leading to retention of configuration. In nonpolar degassed solvents, the halogenation proceeds by a completely nonstereospecific free-radical mechanism. The inversion

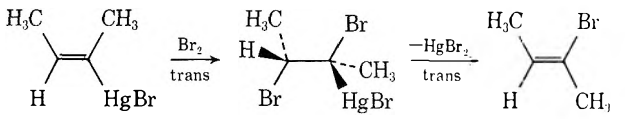
(6) G. M. Whitesides, C. P. Casey, and J. K. Krieger, *J. Amer. Chem. Soc.*, **93**, 1379 (1971).
(7) D. Seyferth and L. G. Vaughan, *J. Amer. Chem. Soc.*, **86**, 883 (1964).
(8) A. S. Dreiding and R. J. Pratt, *J. Amer. Chem. Soc.*, **76**, 1902 (1954).
(9) The stereochemistry of 1-propenyllithium reagents has been determined directly by nmr spectroscopy: D. Seyferth and L. G. Vaughan, *J. Organometal. Chem.*, **1**, 201 (1963).
(10) F. R. Jensen and K. L. Nakamaye, *J. Amer. Chem. Soc.*, **88**, 3437 (1966).
(11) D. Moy, M. Emerson, and J. P. Oliver, *Inorg. Chem.*, **2**, 1261 (1963).
(12) F. R. Jensen and B. Rickborn, "Electrophilic Substitution of Organomercurials," McGraw-Hill, New York, N. Y., 1968, Chapter 4, and references cited therein.

TABLE II
RELATIVE RATES OF BROMINATION IN CARBON DISULFIDE AND PYRIDINE

Registry no.	Compd	Relative rate in CS_2	Relative rate in C_5H_5N
25264-93-1		1.0	1.0
	 (4)	2.2	34
18257-68-6		0.029	0.9

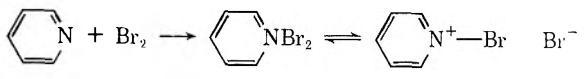
of configuration observed in the bromination of the vinylic mercurials is not compatible with either of the two above mechanisms and must be occurring by a different mechanistic pathway.

The predominant inversion of configuration observed in carbon disulfide can best be explained by a trans addition of bromine to the carbon–carbon double bond of the vinylic mercurial followed by a trans elimination of mercury(II) bromide from the resulting adduct. This addition–elimination mechanism implies that the carbon–carbon double bond is more reactive toward



bromine than is a carbon–mercury bond. If the addition–elimination mechanism is correct, then, by extension, one would expect a vinylic mercurial to be more reactive than an alkyl mercurial in carbon disulfide. The relative rate studies reported in Table II are in agreement with the proposed addition–elimination mechanism. Thus, *trans*-2-butenylmercury(II) bromide, **4**, is about 75 times more reactive toward bromine in carbon disulfide than is *n*-propylmercury(II) bromide. The vinylic mercurial is about 2.2 times more reactive than 1-hexene.

The retention of configuration observed in the bromination of vinylic mercurials in pyridine must be due to direct electrophilic attack of bromine on the carbon–mercury bond. Pyridine interacts strongly both with organomercurials and with bromine; either interaction could lead to the change in mechanism upon changing solvent from carbon disulfide to pyridine. Bromine reacts with pyridine to produce a bromine–pyridine complex[12] which is a more electrophilic brominating agent than bromine. However, the pyridine–bromine complex should be more reactive toward both the



carbon–carbon double bond and the carbon–mercury bond of a vinyl mercurial. Consequently, a change in mechanism would not necessarily be expected upon changing the nature of the electrophile. Pyridine forms complexes with alkylmercury compounds.[12] The electron donation from pyridine to mercury would be expected to activate selectively the carbon–mercury bond of a vinylic mercurial toward reaction with electrophiles. Thus, although in carbon disulfide the carbon–carbon double bond of 1-hexene is 34 times more reactive toward bromine than the carbon–mercury bond of *n*-propylmercury(II) bromide, the two compounds have the same relative reactivity towards bromine in pyridine suggesting an increased relative reactivity of the carbon–mercury bond in pyridine. Similarly, the relative reactivity of *trans*-2-butenylmercury(II) bromide compared with 1-hexene increases from 2.2 to 34 on going from carbon disulfide to pyridine.

The inversion of configuration reported here for the bromination in carbon disulfide of the vinylic mercurials **1**, **2**, **3**, and **4** is surprising, since the extensive research on the halogenation of vinylic mercurials carried out in the research groups of Nesmeyanov and Reutov had previously indicated that halogenation occurred either by a four-center mechanism giving complete retention of stereochemistry or by a totally nonstereospecific free-radical mechanism.[13] The halogenation of vinylic mercurials is normally stereospecific in polar solvents and nonstereospecific in nonpolar solvents. Examples of halogenation occurring with retention of stereochemistry include the bromination of *cis*- and *trans*-stilbenylmercury(II) bromide in dioxane,[14] the iodination of *cis*- and *trans*-β-chlorovinylmercury(II) chloride in methanol, dioxane, or dimethylformamide,[15] and the bromination of *cis*- and *trans*-β-styrylmercury(II) bromide in methanol or dimethyl sulfoxide.[15] In contrast, the same mixture of cis and trans vinylic halides is obtained in the bromination or iodination of *cis*- and *trans*-β-styrylmercury(II) bromide in carbon tetrachloride or in benzene.[15] In a study of the oxymercuration products of allenes, Waters reported that the iodination of *cis*- and *trans*-3-iodomercuri-4-methoxy-2-pentene in carbon tetrachloride and the bromination of *cis*- and *trans*-3-chloromercuri-4-methoxy-2-pentene in pyridine both take place with retention of configuration.[16,17] Thus, the bromination in carbon disulfide of compounds **1**, **2**, **3**, and **4** constitutes the first example so far reported of the inversion of configuration in the halogenation of vinylic mercurials.

The only other examples of inversion of configuration in the halogenation of vinyl metal compounds are found in the chemistry of boron. Matteson[19] has reported that the bromination of *cis*- or *trans*-2-butene-2-boronate gives the vinyl bromide of inverted configuration. The reaction proceeds by the trans addi-

(13) For a recent review of halogenation of vinylic mercurials emphasizing the work of Russian chemists, see L. G. Makarova in "Organometallic Reactions," Vol. I, E. I. Becker and M. Tsutsui, Ed., Wiley, New York, N. Y., 1970, pp 325–345.

(14) A. N. Nesmeyanov and A. E. Borisov, *Tetrahedron*, **1**, 158 (1957).

(15) I. P. Beletskaya, V. I. Karpov, and O. A. Reutov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1707 (1964); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1615 (1964).

(16) W. L. Waters, W. S. Linn, and M. C. Caserio, *J. Amer. Chem. Soc.*, **90**, 6741 (1968).

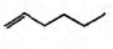
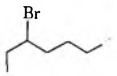
(17) The assignment of stereochemistry of the mercury compounds was made on the assumption that the trans ^{199}Hg–H coupling constant is greater than the cis ^{199}Hg–H coupling constant; this assumption is supported by studies of model compounds.[18] Nonetheless, the assignment may be in error, since the chemical shift of the vinyl hydrogen in the compound assigned the structure *cis*-3-chloromercuri-4-methoxy-2-pentene appears 0.61 ppm downfield from the vinyl hydrogen in the compound assigned the trans structure, although an opposite effect would be expected from the work of Oliver.[11]

(18) W. L. Waters and E. F. Kiefer, *J. Amer. Chem. Soc.*, **89**, 6261 (1967).

(19) D. S. Matteson and J. D. Leidtke, *J. Amer. Chem. Soc.*, **87**, 1526 (1965).

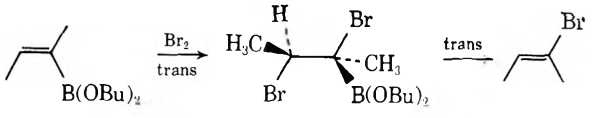
TABLE III

COMPETITION REACTIONS FOR BROMINE IN CARBON DISULFIDE AND PYRIDINE

	Initial concentrations of reactants, 10^2 M				Molar ratio of products			
Solvent				Br_2	2-Bromo-2-butene-			Rate ratio
CS_2		0.56	0.56	0.062		1	32	1:34
CS_2	4.1		5.5	2.2	1.42		1.0	2.2:1
C_5H_5N	7.6	8.5		7.1	29.4	1.0		34:1
C_5H_5N		8.3	9.5	10.4		1.0	1.19[a]	1:1.1

[a] Determined by disappearance of 1-hexene.

tion of bromine to the carbon–carbon double bond to give an isolated intermediate dibromide, which then undergoes a base-catalyzed trans elimination. The



carbon–boron bond is relatively inert to bromine[20] and it is not surprising that the carbon–carbon double bond is attacked preferentially in vinyl boron compounds. Brown[21] has recently shown that the dibromide prepared from a vinylborane decomposes in the presence of base by a trans elimination to give a vinyl bromide of inverted configuration; however, thermal decomposition of the dibromide in carbon tetrachloride proceeded by a cis elimination to give a vinyl bromide of the same configuration as the vinylborane.

Experimental Section

trans-2-**Butenylmercury(II) Bromide.**—Mercury(II) bromide (17.0 g, 0.047 mol) was added to an ether solution of *trans*-2-butenyllithium[6] prepared from *trans*-2-bromo-2-butene (6.4 g, 0.047 mol). The reaction mixture was poured into water and the ether layer was separated, washed with water, dried ($MgSO_4$) and concentrated to 100 ml. Cooling to −78° gave white, lustrous crystals of *trans*-2-butenylmercury(II) bromide (3.5 g, 22% yield): mp 110–113°; $\delta_{TMS}^{CH_2Cl_2}$ 6.25 (quartet of multiplets, J = 6.5 Hz, 1 H, H C=C), 2.01 (quintet, J = 1.5, Hz, 3 H, C=CCH$_3$Hg), and 1.84 (doublet of quartets, J = 6.5, J' = 1.5 Hz, 3 H, CH$_3$C=CHg). Coupling due to ^{199}Hg was also evident: $J_{Hg,\alpha\text{-}CH_3}$ = 188 Hz; $J_{Hg,\beta\text{-}CH_3}$ = 44 Hz.

Anal. Calcd for C_4H_7BrHg: C, 14.32; H, 2.10; Br, 23.81. Found: C, 14.23; H, 2.02; Br, 23.48.

cis-2-**Butenylmercury(II) Bromide.**—Reaction of mercury(II) bromide (9.0 g, 0.024 mol) with an ether solution of *cis*-2-butenyllithium[6] (35 ml, 0.61 N, 0.021 mol, 85% cis) at room temperature for 2 days gave a solution containing a gray, flocculent precipitate. The precipitate was collected and dissolved in 200 ml of methylene chloride. The methylene chloride solution was filtered, dried ($MgSO_4$), and cooled to −78° to give white crystals of *cis*-2-butenylmercury(II) bromide (2.4 g), mp 170–172°. Additional *cis*-2-butenylmercury(II) bromide (1.7 g, 4.1 g total, 57% yield) was isolated from the ether solution: nmr $\delta_{TMS}^{CD_2Cl_2}$ 5.56 (quartet of multiplets, J = 6.5 Hz, 1 H, HC=C), 2.00 (m, 3 H, C=CCH$_3$Hg), and 1.79 (doublet of quartets, J = 6.5, J' = 1 Hz, CH$_3$CH=CHg). Coupling due to ^{199}Hg was evident: $J_{Hg,\alpha\text{-}CH_3}$ = 202, $J_{Hg,\beta\text{-}CH_3}$ = 40 Hz.

Anal. Calcd: C, 14.32; H, 2.10; Br, 23.81. Found: C, 14.23; H, 2.13; Br, 23.52.

trans-1-**Propenylmercury(II) Bromide.**—Reaction of mercury(II) bromide (17.5 g, 0.048 mol) with an ether solution of *trans*-1-propenyllithium[6] (38 ml, 1.25 N, 0.047 mol, 87% trans) at room temperature for 1 hr gave a gray precipitate and a yellow solution. The reaction mixture was poured into 100 ml of water, the solid was dissolved in 100 ml of methylene chloride, and the resulting yellow solution was dried ($MgSO_4$), filtered, and concentrated to 40 ml. Cooling the solution to −10° gave white crystals of *trans*-1-propenylmercury(II) bromide (6.7 g, 43% yield), mp 120–123° (lit.[22] mp 120–121.5°).

cis-1-**Propenylmercury(II) Bromide.**—Reaction of mercury(II) bromide (12.5 g, 0.035 mol) with an ether solution of *cis*-1-propenyllithium[6] (25 ml, 1.32 N, 0.33 mol, 94% cis) at room temperature gave a dark solution. The ether solution was poured into water, separated, washed with water, dried ($MgSO_4$), filtered, and cooled to −78° to give *cis*-1-propenylmercury(II) bromide (3.0 g, 29% yield), mp 60–64°. Recrystallization from 10 ml of ether gave 2.4 g of *cis*-1-propenylmercury(II) bromide, mp 63–67° (lit.[22] mp 62.5–63.5°).

n-**Propylmercury(II) bromide** was prepared by the method of Slotta and Jacob.[23] Reaction of *n*-propylmagnesium bromide (0.31 mol) with mercury(II) bromide (0.40 mol) in ether gave *n*-propylmercury(II) bromide (58.4 g, 0.19 mol, 59%), mp 136–137° (lit.[23] mp 140°).

Reaction of Vinylic Mercury(II) Bromides with Bromine.—When a 0.1 N solution of the vinylic mercury(II) bromide and a 0.1 N solution of bromine in either carbon disulfide, methanol, or pyridine were mixed in the presence of air, the bromine color disappeared immediately. The cis:trans ratio of the vinylic bromides formed was determined by glpc on a 12-ft 15% TCEOP column at 30°. In several cases, yields were determined using decane as an internal vpc standard. The vinylic halides were identified by comparison of glpc retention times with authentic samples. In addition, *trans*-2-bromo-2-butene from the bromination of *cis*-2-butenylmercury(II) bromide in carbon disulfide and *cis*-2-bromo-2-butene from the bromination of *trans*-2-butenylmercury(II) bromide were collected from the gas chromatograph and were identified by comparison of their ir spectra with the ir spectra of authentic samples.

In one case, a solution of *trans*-2-butenylmercury(II) bromide and a solution of bromine in carbon disulfide were placed in opposite arms of an inverted U tube. The solutions were degassed by freezing the solutions with liquid nitrogen, evacuating the apparatus with a vacuum pump, closing the system off from the vacuum line, and melting the solutions. This procedure was repeated five times before the solutions were warmed to room temperature and mixed.

The reactions of bromine with the vinylic mercury(II) bromides are summarized in Table I.

Competition Experiments.—The relative rates of bromination of 1-hexene, *n*-propylmercury(II) bromide, and *trans*-2-butenylmercury(II) bromide, **4**, were determined by competition of the substrates for a deficiency of bromine. Dilute carbon disulfide or pyridine solutions of pairs of the substrates were stirred rapidly at room temperature while a dilute carbon disulfide or pyridine solution of bromine was added slowly by syringe. The relative amounts of 1,2-dibromohexane, *n*-bromopropane and 2-bromo-2-butene were determined by gas chromatography using *n*-octane or *n*-nonane as an internal standard (Table III). The yields of all three products were found to be nearly quantitative in separate bromination experiments.

(20) Tri-*n*-butylborane is not attacked by bromine or iodine in carbon tetrachloride; however, neat bromine attacks both the carbon–boron and the carbon–hydrogen bonds. J. R. Johnson, H. R. Snyder, and M. G. VanCampen, Jr., *J. Amer. Chem. Soc.*, **60**, 115 (1938).

(21) H. C. Brown, D. H. Bowman, S. Misumi, and M. K. Unni, *J. Amer. Chem. Soc.*, **89**, 4531 (1967).

(22) D. Seyferth and L. G. Vaughan, *J. Organometal. Chem.*, **5**, 580 (1966).

(23) K. H. Slotta and K. R. Jacob, *J. Prakt. Chem.*, **120**, 249 (1929).

The relative rates were calculated using the following formula to take into account differences in initial and final concentrations of substrate.

$$\frac{k_A}{k_B} = \frac{\ln A - \ln A_0}{\ln B - \ln B_0}$$

Registry No.—**1**, 6727-46-4; **2**, 6727-44-2; **3**, 40782-37-4; **4**, 40782-38-5; mercury(II) bromide, 7789-47-1; *trans*-2-butenyllithium, 28944-86-7; *cis*-2-butenyllithium, 28944-85-6; *trans*-1-propenyllithium, 6386-72-7; *cis*-1-propenyllithium, 6386-72-7; bromine, 7726-95-6.

Notes

On the Mechanism of the Anthranilate Rearrangement[1]

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Received April 18, 1973

It was reported in 1900 that *o*-nitrotoluene, when heated in aqueous or alcoholic base, rearranged to anthranilic acid.[2] Since then, there has been some experimental work and a good deal of speculation on the mechanism of this reaction. The rearrangement is known not to require molecular oxygen.[3] On tenuous grounds, *o*-nitrobenzoic acid,[3] *o*-nitrosobenzyl alcohol,[4] and anthranil[4] have been proposed as intermediates in reactions involving the uptake of one or two atoms of solvent oxygen. Kukhtenko[5] carried out the rearrangement in [^{18}O]water to distinguish between these latter two possibilities. The molar ratio of base to water was about 1:2, the system was heterogeneous, and the temperature varied from 200 to 150°. He concluded that one atom of solvent oxygen was required.

Out of an interest in the metabolism of such compounds, we considered that Kukhtenko's experiments deserved repetition for two reasons. (1) Despite the lack of experimental information, it was apparent that the rearrangement was carried out under conditions comparable with those reported to cause extensive oxygen exchange in potassium anthranilate.[6] (2) The amount of solvent oxygen incorporated was found to be less than one atom per molecule by an amount greater than the estimated experimental error. Thus, although the results successfully demonstrated that the reaction does not proceed by a pathway using two atoms of solvent oxygen, they ignore the question as to whether the reaction may proceed, in part, by a pathway in which both atoms of the nitro group are transferred to the carboxyl group of anthranilic acid. This latter possibility has been reported to occur in the analogous rearrangement of 2-nitrobenzenesulfenanilide to azobenzenesulfinate.[7]

The base-catalyzed rearrangement of *o*-nitrotoluene was carried out in a 3:1 (v/v) mixture of 2-methoxyethanol and water containing approximately 10% by weight potassium hydroxide. The product was isolated after heating the reactants in an evacuated sealed tube at 100° for 9 hr in the dark. The system was homogeneous and the conditions were less vigorous than those employed previously. The isotopic composition of the carboxyl oxygen atoms was determined from the carbon dioxide formed when the anthranilic acid was quantitatively decarboxylated by heating at 200° *in vacuo*.[8] Normal anthranilic acid decarboxylated according to this procedure[8] showed an oxygen-18 content of 0.206 atom %. The mass spectrum of the carbon dioxide formed from anthranilic acid prepared by rearrangement of *o*-nitrotoluene in water containing 64.1 atom % oxygen-18 is given in Table I.

TABLE I
MASS SPECTRUM OF CARBON DIOXIDE FROM [^{18}O]ANTHRANILIC ACID

m/e	Relative abundance
44	66.1
45	1.70
46	100
47	1.13
48	2.39

The isotopic abundance of oxygen-18 derived from the results in Table I is 31.1 atom %. The low intensity at mass 48 indicates clearly that a negligible amount of *double* oxygen exchange has occurred. Further, if it is assumed that the contribution to mass 48 arises *solely* from exchange of [^{18}O]anthranilate containing one atom of ^{18}O, as is reasonable,[6] the results demonstrate that the rearrangement must proceed to the extent of 95% through the insertion of one atom of oxygen from the solvent water. Since the solvent oxygen is diluted by oxygen released from the nitro group during reaction, the above estimate is a minimal one. If this dilution is allowed for in the formation of anthranilic acid (and other possible products), the data support the above pathway virtually exclusively (99.6%), since it is known that none of the ether, alcohol,[9] or nitro-group[10] oxygen atoms exchanges with water.

This result was checked by measurement of the molecular ion peaks in anthranilic acid. Analysis of the results showed 31.5 atom % oxygen-18 and also that the oxygen-18 was contained in only one of the carboxyl oxygen atoms, which independently supports the above interpretation.

The simplest mechanism consistent with the facts is shown in Scheme I, in which anthranil (1) is an intermediate. It accounts for the incorporation of one atom of oxygen from the solvent. Further, the ionization of

(1) This work was supported in part by the Australian Research Grants Committee. One of us (P. W.) acknowledges a Commonwealth Postgraduate Award.

(2) L. Preuss and A. Binz, *Angew. Chem.*, **16**, 385 (1900).

(3) G. Lock, *Chem. Ber.*, **73B**, 1377 (1940).

(4) R. Scholl, *Monatsh. Chem.*, **34**, 1011 (1913).

(5) I. I. Kukhtenko, *Dokl. Akad. Nauk SSSR*, **132**, 609 (1960).

(6) I. P. Gragerov and M. P. Ponomarchuk, *Zh. Obshch. Khim.*, **29**, 3895 (1959).

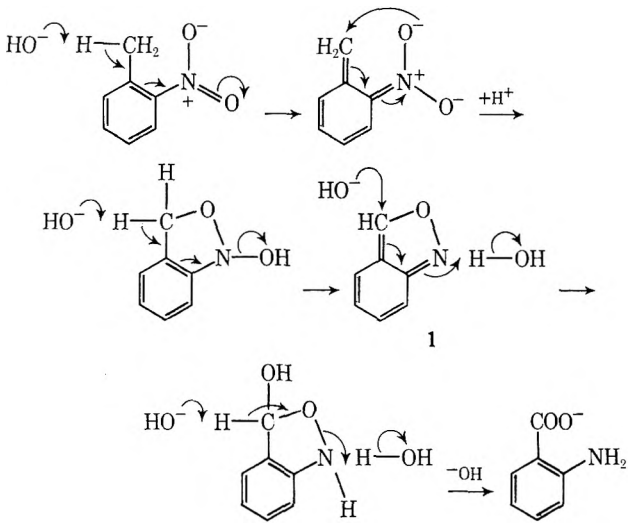
(7) C. Brown, *J. Amer. Chem. Soc.*, **91**, 5832 (1969).

(8) L. W. Clark, *J. Phys. Chem.*, **67**, 138 (1963).

(9) D. Samuel and B. L. Silver, *Advan. Phys. Org. Chem.*, **3**, 123 (1965).

(10) (a) A. Fry and M. Lusser, *J. Org. Chem.*, **31**, 3422 (1966); (b) I. P. Gragerov and A. F. Levit, *Zh. Obshch. Khim.*, **30**, 3726 (1960).

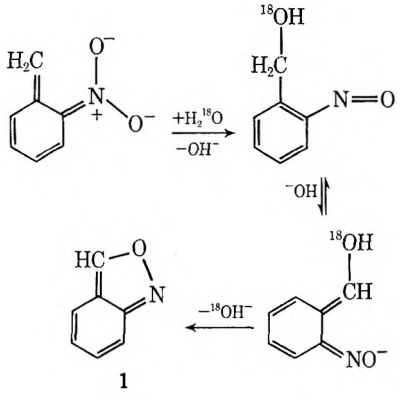
SCHEME I



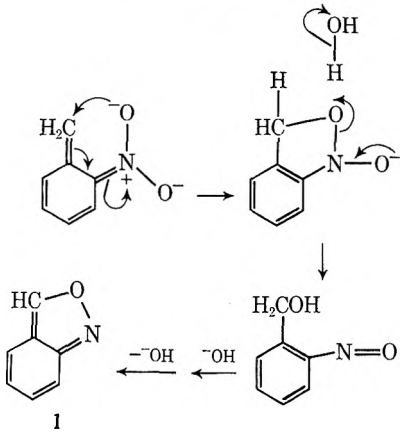
the methyl group and the hydrolysis of anthranil to anthranilic acid are well established.[5,11]

However, while anthranil is a reasonable intermediate, the present work does not comment on the detailed mechanistic pathway to this intermediate. Alternate versions of the mechanism shown, in which only one oxygen atom of the nitro group is transferred to anthranilate, would allow the involvement either of labeled[12] (Scheme II) or unlabeled (Scheme III)

SCHEME II



SCHEME III



(11) M. S. Kharasch, W. G. Brown, and J. McNab, *J. Org. Chem.*, **2**, 36 (1938).

(12) The authors gratefully acknowledge the valuable assistance of a reviewer with this section of the manuscript.

o-nitrosobenzyl alcohol. If *o*-nitrosobenzyl alcohol were an obligatory reaction intermediate and it was possible to remove it from the system as it formed, oxygen-18 analysis may enable a distinction between these latter possibilities.

Experimental Section

o-Nitrotoluene was fractionally distilled twice, the second distillation being performed under dry nitrogen, bp 94° (9.3 mm) [lit.[13] bp 94° (9.3 mm)]. 2-Methoxyethanol was redistilled three times, bp 124° (lit.[14] bp 124.4°). [^{18}O]Water (81.52 atom % ^{18}O, 0.254 atom % ^{17}O, 83.7 atom % D) was supplied by Yeda Research and Development Co., Rehovoth, Israel.

Rearrangement of *o*-Nitrotoluene in [^{18}O]Water.—*o*-Nitrotoluene (0.511 g) and potassium hydroxide (0.591 g, Baker Analyzed Reagent) were mixed with [^{18}O]water (1.071 g) and 2-methoxyethanol (3 ml). The reaction vessel was flushed rapidly with dry nitrogen, the contents were frozen, and the vessel was evacuated and sealed. The reaction was allowed to proceed for 9 hr at 100° in the dark. After the solvent was removed *in vacuo*, the residue was dissolved in water and extracted with ether. The pH was reduced to 3.4 and the extraction was repeated. This fraction was dried (Na_2SO_4), the solvent was removed, and the product was sublimed *in vacuo* to give 53 mg (10.4%) of anthranilic acid, mp 136.5–139°. Recrystallization from ether–hexane and benzene–hexane gave anthranilic acid, mp 143.8–144.2° (lit.[3] mp 145.5°). This purification procedure ensured that the product was in contact with normal water for only 30 min, under conditions unlikely to cause exchange.

Anthranilic acid was decarboxylated by heating *in vacuo* at 200–220° for 30–45 min and the carbon dioxide was purified by distillation from −80 to −196°. Isotopic ratios were measured in a Nier-type mass spectrometer.[15] The mass spectrum of anthranilic acid was determined on an AEI MS902 spectrometer at 70 eV using the direct insertion probe.

Registry No.—*o*-Nitrotoluene, 88-72-2; anthranilic acid, 118-92-3.

(13) J. Timmermans, "Physico-Chemical Constants of Pure Organic Compounds," Elsevier, New York, N. Y., 1950, p 594.

(14) J. A. Riddick and E. E. Toops, Jr., "Organic Solvents, Physical Properties and Methods of Purification," 2nd ed, Interscience, New York, N. Y., 1955, p 249.

(15) (a) A. O. Nier, *Rev. Sci. Instrum.*, **18**, 398 (1947); (b) A. O. Nier, *Phys. Rev.*, **77**, 789 (1950).

A New Synthesis of Benzocyclobutene and Bicyclo[4.2.0]octa-1(6),3-diene

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Received March 19, 1973

There are several methods available for the synthesis of benzocyclobutene[2] (**1**). We required large quantities of **1** and were not satisfied with presently published methods such as the improved pyrolysis of 1,3-dihydroisothionaphthene 2,2-dioxide (**2**).[3] We were not satisfied with this route as it involved the use of rather noxious compounds as synthetic intermediates and special apparatus for the final thermal decomposition. We also had a need for large amounts of bicyclo[4.2.0]octa-1(6),3-diene (**3**). We therefore have de-

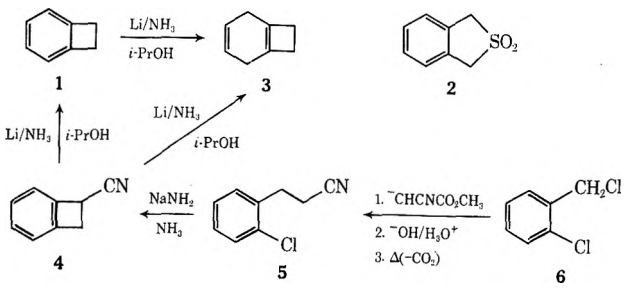
(1) Fellow of the Alfred P. Sloan Foundation.

(2) I. Klundt, *Chem. Rev.*, **70**, 471 (1970).

(3) J. Oliver and P. Ongley, *Chem. Ind. (London)*, 1024 (1965).

veloped a simple new synthetic route to both **1** and **3** which is of acceptable yield and amenable to large-scale production.

1 is prepared in 83% yield from 1-cyanobenzocyclobutene[4] (**4**) *via* reduction with Li in liquid ammonia. This is a useful example of the unusual reductive cleavage of a benzylic nitrile.[5] The nitrile **4** is readily prepared by the method of Bunnett and Skorcz as outlined above from *o*-chlorobenzyl chloride. We routinely effect the **6** → **5** → **4** conversion in 48% overall yield starting with as much as 1 kg of **6**.



While **3** is a known compound[6] it was prepared *via* an involved route. The Birch reduction of **1** has never been reported and we find that it proceeds to give **3** in excellent yield (98%). In fact, one can proceed directly from **4** to **3** without isolating **1** simply by adding the appropriate additional amounts of Li and isopropyl alcohol.

There are several dihydrobenzocyclobutene double bond isomers that could have resulted as products from the Birch reduction of **1**. In fact, the unusual chemical nature of carbocyclic four-membered rings does not permit one to predict the product with any great certainty. It is interesting that this reaction proceeds so easily and cleanly to give the double bond arrangement as in **3**. This new synthesis of benzocyclobutene and its subsequent Birch reduction to **3** may provide a ready access to some potentially new and interesting compounds.

Experimental Section

Preparation of Benzocyclobutene from 1-Cyanobenzocyclobutene (1).—A 3-l. three-necked flask, equipped with mechanical stirrer and gas inlet and outlet, was flame dried under a vigorous nitrogen flow. Ammonia (*ca.* 1.75 l.) was condensed and a solution of 1-cyanobenzocyclobutene (77.4 g, 0.6 mol) and isopropyl alcohol (72 g, 1.2 mol) in diethyl ether (300 ml) was added. The temperature was maintained at −40 to −45° and lithium wire (7.91 g, 1.14 mol) was added over a 30-min period. When all the lithium has reacted, ammonium chloride (64.0 g, 1.2 mol) was added while the temperature was kept below the boiling point of ammonia with a Dry Ice–acetone bath. The ammonia was evaporated overnight and water (1.5 l.) was added to the residue. The organic products were extracted with diethyl ether (4 × 300 ml), and this solution was washed successively with water (1 l.), 3 *N* hydrochloric acid (500 ml), saturated sodium bicarbonate solution (200 ml), and saturated sodium chloride solution (200 ml) and dried over magnesium sulfate. After filtration and concentration, distillation of the residue afforded benzocyclobutene (41.0 g), bp 79–83° (95 mm), 82.5% based on recovered starting material, and 1-cyanobenzocyclobutene (15.7 g), bp 75–78° (1 mm). Integration of the nmr spectrum showed the benzocyclobutene to be contaminated with bicyclo[4.2.0]octa-1(6),3-diene only to the extent of 3%: nmr (CCl_4) τ 6.88 (s, 4 H), 3.0 (A_2B_2, 4 H).

Preparation of Bicyclo[4.2.0]octa-1(6),3-diene from Benzocyclobutene (3).—A 1-l. three-necked flask was equipped with a Dry Ice condenser, mechanical stirrer, and gas inlets and outlet and was flame dried under a vigorous nitrogen flow. Ammonia (400 ml) was condensed. A solution of benzocyclobutene (13.0 g, 0.125 mol), isopropyl alcohol (15 ml), and tetrahydrofuran (50 ml, freshly distilled from lithium aluminum hydride) was added. Lithium wire (2.5 g, 0.36 mol) was added over a period of 2 hr. At this point the nmr of an aliquot showed no remaining aromatic protons. Ammonium chloride (18.7 g, 0.36 mol) was added cautiously and the ammonia was evaporated. Water (100 ml) was added to the residue and the organic product was extracted with diethyl ether (3 × 100 ml).

The ethereal solution was washed with water (2 × 100 ml) and saturated sodium chloride solution (2 × 50 ml), dried over magnesium sulfate, filtered, and concentrated. Distillation of the residue gave 12.78 g (98%) of the bicyclo[4.2.0]octa-1(6),3-diene: bp 78–79° (90 mm); nmr (CCl_4) τ 4.33 (s, 2 H), 7.50 (s, 8 H).

Acknowledgment.—This investigation was supported by a Public Health Service Research Career Development Award (GM-70,394-01) from the Institute of General Medical Sciences.

Registry No.—**1**, 694-87-1; **3**, 38325-66-5; **4**, 6809-91-2.

(4) J. Skorcz, *et al.*, *J. Med. Chem.*, **9**, 656 (1966).

(5) P. Arapakos, M. Scott, and F. Huber, Jr., *J. Amer. Chem. Soc.*, **91**, 2059 (1969).

(6) J. Garrett and G. Fonken, *Tetrahedron Lett.*, 191 (1969).

Prostaglandins. A Total Synthesis of (±)-11,15-Dideoxy-PGE$_2$ and (±)-11-Deoxy-PGE$_2$ Methyl Ester

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Received April 30, 1973

The synthesis of deoxyprostaglandins which represent potential intermediates for conversion into the naturally occurring prostaglandins *via* microbiological hydroxylation has recently been the subject of considerable synthetic effort. During the course of our work, a number of alternate 11-deoxy-PGE$_2$ syntheses have been developed.[1] We wish to report practical syntheses of (±)-11,15-dideoxyprostaglandin E$_2$ (**2**) and (±)-11-deoxyprostaglandin E$_2$ methyl ester (**1**).

The readily available cyclopentenone **7b** (*vide infra*) plus the recently reported capabilities of appropriately functionalized organocopper reagents to undergo smooth 1,4 conjugate addition to cyclopentenones[2] have allowed us to develop a short route to the deoxyprostaglandins of the E$_2$ series. Previous approaches to (±)-11-deoxy-PGE$_2$ methyl ester have constructed the C$_8$ side chain from dimethyl 2-oxoheptylphosphonate,[3] which was originally introduced by Corey.[4]

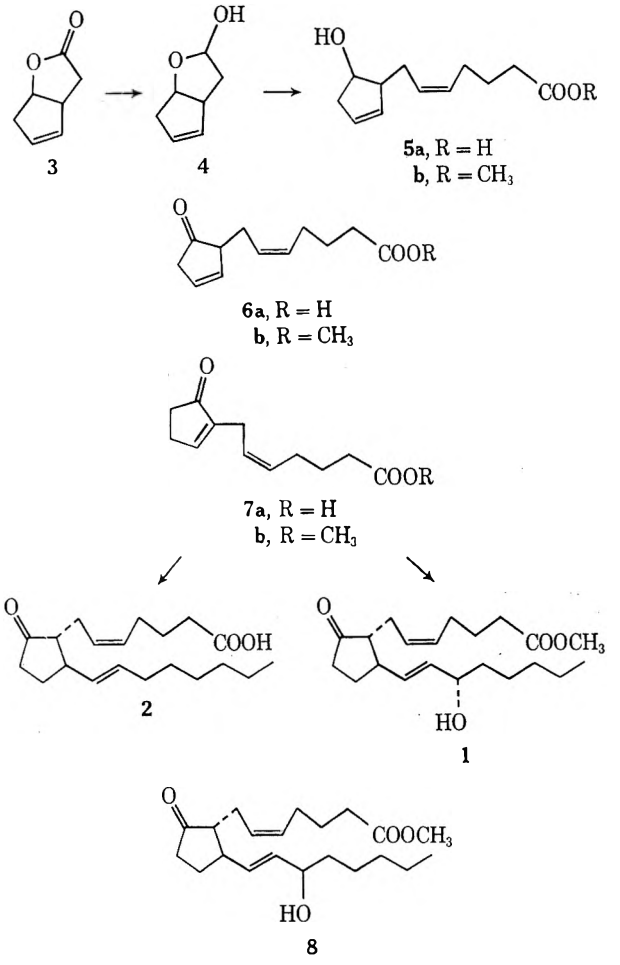
We now describe the synthetic sequence. Reduction

(1) P. Crabbé and A. Guzman, *Tetrahedron Lett.*, 115 (1972); J. Bagli and T. Bogri, *ibid.*, 3815 (1972); K. F. Bernady and M. J. Weiss, *ibid.*, 4083 (1972).

(2) (a) C. J. Sih, P. Price, R. Sood, R. G. Salomon, G. Peruzzotti, and M. Casey, *J. Amer. Chem. Soc.*, **94**, 3643 (1972); (b) A. F. Kluge, K. G. Untch, and J. H. Fried, *ibid.*, **94**, 7827 (1972).

(3) For a versatile synthesis of dimethyl 2-oxoalkylphosphonates see P. A. Grieco and C. S. Pogonowski, *J. Amer. Chem. Soc.*, **95**, 3071 (1973).

(4) E. J. Corey, I. Vlattas, N. H. Andersen, and K. Harding, *J. Amer. Chem. Soc.*, **90**, 3247 (1968).



of lactone **3**[5] with dissobutylaluminum hydride in toluene as previously described[6] affords a quantitative yield of hemiacetal **4**. The cis double bond in **5a** was introduced in 80% yield by treatment of hemiacetal **4** with the ylide derived from 5-triphenylphosphoniopentanoic acid and sodio methylsulfinylmethide in dimethyl sulfoxide.[7] The resulting acid **5a** was characterized as its methyl ester **5b** (ethereal diazomethane). Alcohol **5a** was oxidized with Jones reagent at 0° in acetone to afford a 98% yield of the corresponding Δ^3-cyclopentenone **6a** which was immediately isomerized in 85% yield to the more stable α,β-unsaturated ketone **7a** by treatment with 95% ethanol–1 *N* NaOH (1:1) at 35–40° for 1 hr. Esterification with diazomethane produced ester **7b**. Treatment of **7b** with 3-(α-ethoxy)ethoxy-1-lithio-*trans*-oct-1-ene in the presence of tri-*n*-butylphosphine–copper(I) iodide complex at −78° in ether for 1 hr followed by warming to 0° afforded after removal of the C-15 protecting group (HOAc–THF–H_2O) two *dl* pairs in approximately equal amounts. The stereochemistry at C-8 and C-12 was anticipated as a result of protonation of the resultant enolate to give the thermodynamically more stable trans arrangements of alkyl and vinyl groups. Separation by preparative thin layer chromatography afforded pure (±)-11-deoxy-PGE_2 methyl ester (**1**) which exhibited satisfactory nmr, ir, and mass spectral data. In addition it showed identical tlc behavior in several solvent systems with an authentic sample. There was obtained also (±)-11-deoxy-15-epi-PGE_2 methyl ester (**8**).

Similarly, when **7b** was treated with 2 molar equiv of 1-lithio-*trans*-oct-1-ene in the presence of 1 molar equiv of tri-*n*-butylphosphine–copper(I) iodide complex, there was obtained after ester hydrolysis (±)-11,15-dideoxy-PGE_2 (**2**) which exhibited identical tlc behavior with an authentic sample.

(5) E. J. Corey, Z. Arnold, and J. Hutton, *Tetrahedron Lett.*, 307 (1970).
(6) P. A. Grieco, *J. Org. Chem.*, **37**, 2363 (1972).
(7) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963); E. Hamanaka, Ph.D. Thesis, Harvard University, 1967. The cis geometry for the double bond in V is indicated by the absence of the absorption characteristic of trans CH=CH at 10.3–10.4 μ.

Experimental Section

Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Precoated plc silica gel F-254 Merck plates were used for preparative tlc. The following spectrometers were used: nmr, Varian A-60D and T-60; ir, Perkin-Elmer Model 247; mass spectrum, LKB-9.

2-(Methyl-*cis*-hept-2-en-7-oate)cyclopent-3-en-1-ol (5b).—Triphenylphosphoniopentanoic acid, 13.5 g (30.5 mmol) (prepared from 5-bromopentanoic acid and triphenylphosphine in acetonitrile), was dried at 75° (0.1 mm) for 1 hr. The acid was then dissolved in 60 ml of dimethyl sulfoxide (DMSO, freshly distilled from CaH_2). To this solution under an atmosphere of nitrogen was added 46.0 mmol of sodium methylsulfinylmethide which was prepared from 1.94 g (46.0 mmol) of sodium hydride dispersion (57%) and 40 ml of dry DMSO. To the resultant ylide solution was added 1.50 g (11.8 mmol) of pure hemiacetal **4** in 3 ml of dry DMSO. Stirring at room temperature was continued for 2.5 hr, after which time the DMSO was removed under reduced pressure and the residue was taken up in 100 ml of water. The resultant aqueous solution was extracted with ether–ethyl acetate (1:1) to remove any neutral compounds, acidified to pH 2.0, and extracted several times with pentane–ether (1:1). The combined organic layers were washed with brine and separated and the solvent was removed under reduced pressure to leave 2.40 g (90%). The acid **5a** was characterized as its methyl ester **5b** (ethereal diazomethane). The crude ester was evaporatively distilled, 106–110° (0.01 mm), affording 1.88 g (71%) of a homogeneous material: ν_{max} ($CHCl_3$) 1735 cm^{-1}; nmr (CCl_4) δ 5.8–5.2 (m, 4 H), 4.5–4.15 (m, 1 H), 3.6 (s, 3 H); *m/e* 224.

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.43; H, 9.01.

2-(Methyl-*cis*-hept-2-en-7-oate)-2-cyclopentenone (7b).—A solution of 1.0 g of alcohol **5a** in 35 ml of acetone was cooled to 0° and treated dropwise with 2.6 ml of standard Jones reagent. After 5 min, the reaction was quenched with isopropyl alcohol and the acetone was removed under reduced pressure. The resultant residue was taken up in water and extracted with ether several times. The combined ethereal extracts were washed with water, and saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Removal of the solvent *in vacuo* afforded 1.00 g (99% yield) of Δ^3-cyclopentenone (**6a**) [ν_{max} ($CHCl_3$) 3600–2400, 1740 (C=O), 1705 cm^{-1} (COOH)], which was characterized as its methyl ester **6b** (diazomethane) [ν_{max} ($CHCl_3$) 1740 cm^{-1}; nmr (CCl_4) δ 3.64 (s, 3 H), 5.40 (m, 2 H), 6.08 (s, 2 H); *m/e* 222].

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.32; H, 8.08.

The Δ^3-cyclopentenonecarboxylic acid **6a** was dissolved in 50 ml of 95% ethanol. To this solution was added 70 ml of 1 *N* NaOH and the resultant homogeneous solution was heated at 35°. After 2.5 hr, the reaction mixture was concentrated *in vacuo* and the crude product was dissolved in 25 ml of water. The resultant aqueous solution was extracted with ethyl acetate and acidified with 1 *N* HCl, and the product was isolated by extraction with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure afforded 1.0 g of crude acid **7a** which was esterified with diazomethane, producing 970 mg (92%) of pure enone ester **7b** [ν_{max} ($CHCl_3$) 1725, 1695, 1630 cm^{-1}; nmr (CCl_4) δ 7.15 (m, 1 H), 5.41 (m, 2 H), 3.60 (s, 3 H); *m/e* 222].

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.94; H, 7.81.

(±)-11,15-Dideoxyprostaglandin E_2 (2).—To a suspension of 393 mg (1 mmol) of tri-*n*-butylphosphine–copper(I) iodide (freshly prepared) in 5 ml of anhydrous ether cooled to −78° under an atmosphere of nitrogen was added with stirring a solution of 1-lithio-*trans*-oct-1-ene in anhydrous ether [prepared by treatment of 1-iodo-*trans*-oct-1-ene (476 mg, 2 mmol) in 3 ml of anhydrous ether cooled to −78° with 2.86 ml of *tert*-butyllithium (1.44 *M* in *n*-pentane) followed by stirring for an additional 2 hr]. The resulting mixture was stirred for approximately 45 min at −78° and then was treated with 220 mg (1 mmol) of cyclopentenone **7b** in 1 ml of ether. After the addition was complete, the reaction was warmed to 0° and stirring at that temperature was continued for 2 hr. The reaction was quenched by the addition of aqueous ammonium sulfate and the product was isolated by extraction with ether. Purification by preparative tlc afforded 154 mg (47%) of (±)-11,15-dideoxy-PGE_2 methyl ether [ν_{max} ($CHCl_3$) 1740, 970 cm^{-1}; nmr (CCl_4) δ 3.62 (s, 3 H, CH_3), 5.20–5.60 (m, 4 H, olefinic); *m/e* 334].

A solution of (±)-11,15-dideoxy-PGE_2 methyl ester (25 mg) in 1.2 ml of THF and 0.5 ml of water containing 1.0 ml of 0.1 *N* NaOH was stirred at room temperature for 24 hr. Work-up afforded 20 mg of pure (±)-11,15-dideoxy-PGE_2 (2) which was chromatographically identical in several solvent systems with a sample kindly provided by Dr. M. J. Weiss (Lederle Laboratories).

(±)-11-Deoxyprostaglandin E_2 Methyl Ester (1).—To a mixture of 393 mg (1 mmol) of tri-*n*-butylphosphine–copper(I) iodide in 7 ml of anhydrous ether cooled to −78° maintained under a nitrogen atmosphere was added with stirring a solution of 3-(α-ethoxy)ethoxy-1-lithio-*trans*-oct-1-ene in anhydrous ether [prepared by treatment of 3-(α-ethoxy)ethoxy-1-iodo-*trans*-oct-1-ene[8] (652 mg, 2 mmol) in 5 ml of anhydrous ether cooled to −78° with 2.86 ml of *tert*-butyllithium (1.44 *M* in *n*-pentane); the solution was maintained at −78° for 1.75 hr]. The resulting mixture was stirred at −78° for 60 min and then was treated with 222 mg (1 mmol) of cyclopentenone (**7b**) in 5 ml of anhydrous ether. The reaction mixture was stirred at −78° for an additional 30 min and then warmed to 0°, where stirring was continued for 1.5 hr. The reaction was quenched by the addition of aqueous ammonium sulfate and the product was extracted with ether. The combined ether extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on silica gel. There was obtained 90 mg (21%) of product plus 30 mg of recovered **7b**.

A solution of the above material (90 mg) in 0.2 ml of THF was added to 1.75 ml of acetic acid–water (65:35). The resulting solution was heated at 39° for 6 hr. After cooling, the product was isolated by extraction with ether. The combined ether layers were washed with saturated sodium bicarbonate solution and water and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure afforded 56 mg of (±)-11-deoxy-PGE_2 methyl ester (1) and (±)-11-deoxy-15-epi-PGE_2 methyl ester (8), which appeared to be present in equal amounts as indicated by tlc. Chromatography by preparative thin layer with ethyl acetate–hexane (1:2) afforded 18 mg of (±)-11-deoxy-PGE_2 methyl ester [ν_{max} $CHCl_3$ 3610, 3460, 1730, 970 cm^{-1}; nmr (CCl_4) δ 5.20–5.70 (m, 4 H, olefinic), 4.00 (m, 1 H), 3.62 (s, 3 H, OCH_3); *m/e* 350]. (±)-11-Deoxy-PGE_2 methyl ester was chromatographically identical in several solvent systems with a sample kindly provided by Dr. J. F. Bagli (Ayerst Laboratories).

Acknowledgment.—This research was supported by the Health Research and Services Foundation (HRSF), Pittsburgh, Pa. We thank Dr. J. F. Bagli for providing us with a sample of (±)-11-deoxy-PGE_2 methyl ester and Dr. M. J. Weiss for a sample of (±)-11,15-dideoxy-PGE_2.

Registry No.—1, 35120-22-0; 2, 40098-57-5; 4, 34638-26-1; 5a, 40899-59-0; 5b, 40899-60-3; 6a, 40899-61-4; 6b, 40899-62-5; 7a, 40899-63-6; 7b, 38698-54-3; triphenylphosphoniopentanoic acid, 39968-97-3; 1-lithio-*trans*-oct-1-ene, 37730-25-9; 3-(α-ethoxy)ethoxy-1-lithio-*trans*-oct-1-ene, 38380-59-5.

(8) Prepared by treatment of *trans*-1-iodo-1-octen-3-ol[2b] in methylene chloride containing a catalytic amount of *p*-toluenesulfonic acid at 0° with a slight excess of freshly distilled ethyl vinyl ether.

Biosynthesis of Phenazines. II. Incorporation of [6-^{14}C]-D-Shikimic Acid into Phenazine-1-carboxylic Acid and Iodinin[1]

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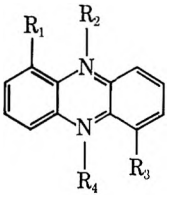
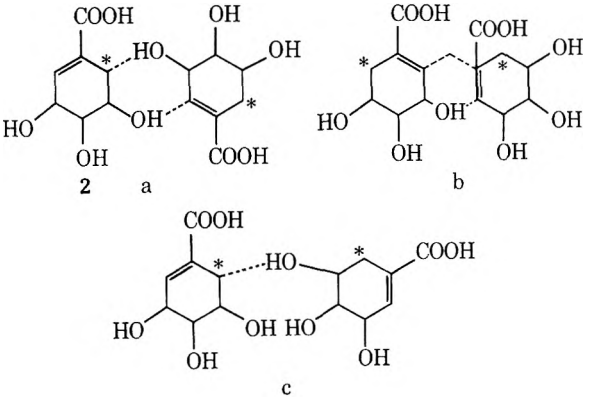
Received April 12, 1973

Previously[1] we have shown that shikimic acid is incorporated into phenazine-1-carboxylic acid (**1a**) and into pyocyanine (**1b**). Degradation of these metabolites[1] from feeding with [G-^{14}C]shikimic acid (**2**) was in agreement with incorporation of the intact shikimic acid molecule. Results from [1,6-^{14}C]shikimic acid feedings narrowed the number of pairing possibilities of two shikimic acid molecules down to four.[1]



1a, R_1 = COOH; R_2 = R_4 = lone pair; R_3 = H
b, R_1 = O^-; R_2 = lone pair; R_3 = H; R_4 = $^+CH_3$
c, R_1 = R_3 = OH; R_2 = R_4 = →O

We have now obtained a sample of [6-^{14}C]-D-shikimic acid,[2] which allowed us to narrow down the number of possible pairing schemes. Feeding of this precursor to *Pseudomonas aureofaciens* led to a 36% incorporation into phenazine-1-carboxylic acid. The labeling data, as shown in Table I, further narrow the number of pairing schemes of two shikimic acid molecules from four to two, *viz.*, d and e. It was hoped that feeding with [$^{14}C_6$]-D-shikimic acid would also allow us to distinguish between the pairing schemes proposed for iodinin by Gerber[3] (a), Holliman[4] (b), and us[1] (c),



since our previous data[1] were not in agreement with the pairing schemes suggested in ref 3 and 4.

The three pairing schemes a–c can be distinguished by 6-monolabeled shikimic acid (Table II). This was

(1) Part I: U. Hollstein and L. G. Marshall, *J. Org. Chem.*, **37**, 3510 (1972).
(2) K. H. Scharf and M. H. Zenk, *J. Label. Compounds*, **7**, 525 (1971).
(3) M. Podojil and N. N. Gerber, *Biochemistry*, **9**, 4616 (1970).
(4) R. B. Herbert, F. G. Holliman, and D. N. Ibberson, *J. Chem. Soc., Chem. Commun.*, 355 (1972).

TABLE I
LABELING RESULTS

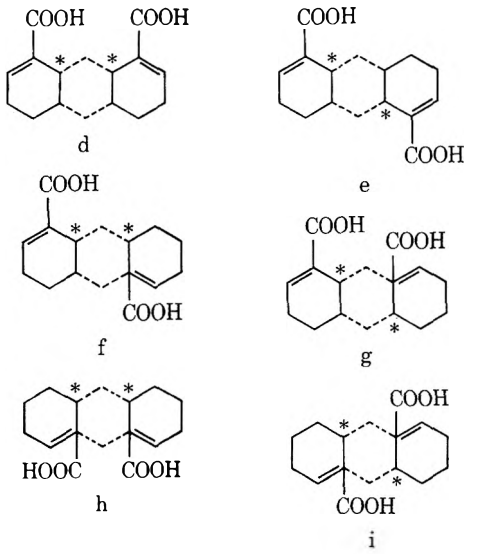
Compd	Feeding of [6-^{14}C]-D-shikimic acid to *Ps. aureofaciens*: dpm/mmol	Found, %	Calcd,[a] %	*Chr. iodinum*: dpm/mmol	Found, %	Calcd,[b] %
Phenazine-1-carboxylic acid	303,000	100	100			
CO_2 (from C_1-COOH)	680	0.2	0			
Phenazine	291,000	96.1	100			
Iodinin				448,000	100	100
1,6-Dihydroxyphenazine				443,000	96.7	100
Pyrazinetetracarboxylic acid	302,000	99.6	100	455,000	101.6	100
Pyrazine	309,000	101.6	100	464,000	103.6	100
CO_2	3,560	1.2	0	55,680	12.4	0

[a] For pairing schemes d and e. [b] For pairing schemes d–i.

TABLE II
DIFFERENT PAIRING SCHEMES FOR IODININ

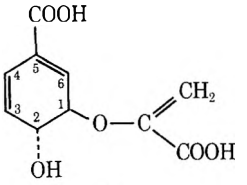
	Specific activity (%) for a (Gerber)	b (Holliman)	c (Hollstein)
Iodinin	100	100	100
Pyrazinetetracarboxylic acid	50	50	100
Pyrazine	50	0	50
CO_2	0	50	50

not possible with the 1,6-dilabeled precursor. Our data (Table I) clearly show that the pairing scheme cannot be a, b, or c. Six pairing schemes (d–i) can be written to accommodate our data. Of these, only d and c are identical with those deduced for phenazine-1-carboxylic acid. Assuming that the hydroxyls in iodinin are generated in an identical manner in both rings, schemes d, f, g, h, and i must be excluded. It



is to be noted that none of the set d–i can accommodate Gerber's data for the [1,6-^{14}C]shikimic acid generated iodinin.[3]

Recently it was demonstrated that chorismic acid[5] (**3**) is an intermediate in the pathway leading to pyocyanine and that it represents also the point in the general aromatic pathway at which the route to pyocyanine branches off.[6] It may be inferred that



3

chorismic acid is also the precursor for phenazine-1-carboxylic acid since pyocyanine is generated from phenazine-1-carboxylic acid[7] and possibly for iodinin. Thus, the proposed schemes for iodinin where one of the hydroxyls comes from the C_3–OH in shikimic acid[1,4] are no longer valid. Chorismic acid has no hydroxyl at the position corresponding to C_3 of shikimic acid.

Based on the foregoing we propose that the biosynthesis of the phenazine skeleton proceeds *via* two identical C_6- or C_1-N-substituted chorismic acids. Introduction of nitrogen at C_6, either initially into chorismic acid or by a C_1-N-substituted chorismic acid during the formation of the tricyclic ring system, would be analogous to the formation of anthranilic acid from chorismic acid. Further work on these aspects is in progress.

Experimental Section

Melting points were obtained on a Kofler hot stage apparatus. Counting was done with a Beckman liquid scintillation spectrometer. Electronic spectral determinations were made with a Cary recording spectrophotometer. The degradation of phenazine-1-carboxylic acid, the determination of specific activities and various scintillation solutions have been previously described.[1]

Microorganisms and Pigment Production.—*Pseudomonas aureofaciens*, ATCC 13985, was maintained, grown, and extracted as described.[1] *Chromobacterium iodinum* was obtained from the collection of Dr. Waksman, strain 26, Rutgers University. From the same strain ATCC maintains *Ps. iodinum* 15728 (IMRU 26). The integrity and viability of the culture was preserved by monthly transfers to new slants. Storage slants were made of an aqueous solution of 1% glucose (Difco), 1% yeast extract (Difco), and 1.5% Agar (Difco). The production and inoculum medium consisted of the same solution without the Agar. Fifty milliliters of inoculum medium was autoclaved in a 250-ml flask, which was loop inoculated from the storage slant and placed on an Eberbach shaker, rotating through an orbit of 2 in., 60 times/min, at 26°. After growing for 24 hr, 2 ml of the inoculum solution was added to 650 ml of production medium of the same nutrient composition in a 2800-ml Fernbach flask. The characteristic purple color of iodinin appeared after about 50–60 hr. After a total production period of about 70 hr, the suspension was extracted with an equal

(5) The numbering conforms to the formulation α-(5-carboxyl-1,2-dihydro-2-hydroxyphenoxy)acrylic acid.

(6) R. P. Longley, J. E. Halliwell, J. J. R. Campbell, and W. M. Ingledew, *Can. J. Microbiol.*, **18**, 1357 (1972).

(7) M. E. Flood, R. B. Herbert, and F. G. Holliman, *J. Chem. Soc., Perkin Trans. 1*, **1**, 622 (1972).

volume of chloroform, and the resulting emulsions were broken up by centrifuging. Per 650 ml of production medium about 110 mg of iodinin was obtained, $\lambda_{max}^{CHCl_3}$ 530 nm (ϵ 6300) [reported[8] 530 nm (ϵ 6340)] and mp 236° dec (reported[9] 224–225° dec).

Labeled Feeding and Extraction of Active Pigments.—[6-^{14}C]-D-Shikimic acid (1 μCi, 35.6 μCi/μmol) was fed in two equal portions under sterile conditions to two 1-l. production media of *Ps. aureofaciens* each in a 2800-ml Fernbach flask, which had been grown for 12 hr at 28.5°. Growth was continued for 12 hr and phenazine-1-carboxylic acid extracted and purified as described.[1] The yield was 151 mg. The material showed an incorporation of 36% (100 × total activity isolated over total activity fed). It was diluted 3.56 times in chloroform with inactive phenazine-1-carboxylic acid.

After 44 hr of growth 1 μCi of [6-^{14}C]-D-shikimic acid was added under sterile conditions in two equal portions to each of two 650-ml production media of *Chr. iodinum*, when the characteristic purple color of iodinin was not yet apparent. The color appeared at 46 hr. Growth was continued for another 32 hr and the pigment was extracted after a total of 78 hr: yield 206 mg, 34% incorporation of fed activity. The compound was diluted 2.00 times in pyridine with inactive iodinin, obtained from previous inactive productions.

1,6-Dihydroxyphenazine from Iodinin.—Iodinin (200 mg) in 100 ml of dioxane (AR) were added to 200 mg of reduced PtO_2 in 50 ml of dioxane. Reduction at atmospheric pressure and room temperature was complete in 30 min after an uptake of 3 mol of H_2. The colorless solution, presumably of 1,6-dihydroxy-5,10-dihydrophenazine, was filtered whereupon it rapidly turned yellow. Upon passing O_2 through the solution a golden yellow color was soon attained. Evaporation yielded 171 mg (98%) of gold-brown crystals of 1,6-dihydroxyphenazine, mp 271–278° (reported[10] 274°).

Pyrazinetetracarboxylic Acid from 1,6-Dihydroxyphenazine.—A 109-mg sample was oxidized in 2 ml of 1% KOH with 7.7 ml of 17% hot $KMnO_4$ as described,[1] in 45% yield.

Acknowledgments.—This work was supported by Grant No. A109598, National Institutes of Health. We wish to thank Dr. M. H. Zenk, Department of Plant Physiology, Ruhr University, Bochum, Germany, for the gift of [6-^{14}C]-D-shikimic acid, and Dr. Ruth E. Gordon, Institute of Microbiology, Rutgers University, N. J., for a strain of *Chromobacterium iodinum*.

Registry No.—1a, 2538-68-3; 1c, 68-81-5; 2, 138-59-0.

(8) N. Gerber and M. P. LeChevalier, *Biochemistry*, **3**, 598 (1964).
(9) H. P. Sigg, *Helv. Chim. Acta*, **50**, 716 (1967).
(10) H. Akabori and M. Nakamura, *J. Antibiotics (Tokyo) Ser. A*, **12**, 17 (1959).

Nucleophilic Displacement Reactions on 4-Bromoisophorone

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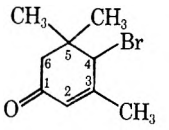
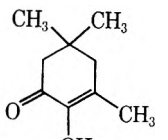
Received March 27, 1973

Marx and coworkers[1] have recently reported their work of nucleophilic displacements on 4-bromoisophorone (**1**) with NaOH and silver acetate. They obtained the 2-substituted products (**2** and **3**) in addition to other materials and no 4-substituted derivatives (**4a** and **4b**) as earlier reported.[2] Based upon the results of the earlier workers, we had hoped to prepare several 4-thio and 4-sulfonyl derivatives of isophorone



1



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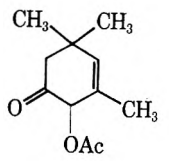

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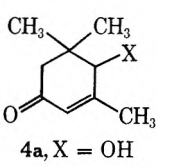
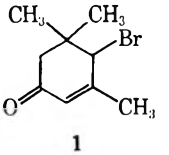


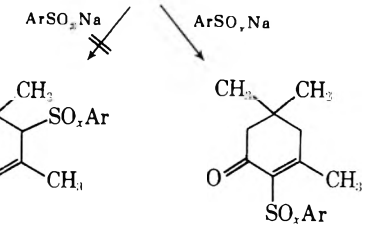
4a, X = OH
b, X = OAc

(**5** and **6**) *via* nucleophilic displacement upon 4-bromoisophorone as shown in Scheme I. The products obtained, however, were the 2-substituted materials **7** and **8**.

SCHEME I



1



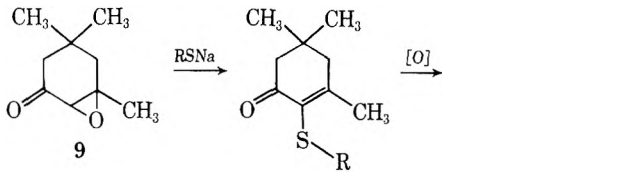
5, Ar = *p*-$CH_3C_6H_4$; *x* = 0 **7**, Ar = *p*-$CH_3C_6H_4$; *x* = 0
6, Ar = *p*-$CH_3C_6H_4$; *x* = 2 **8**, Ar = *p*-$CH_3C_6H_4$; *x* = 2

The structural assignments of these products were based on nmr and ir analyses and alternate synthesis. The nmr data given in the Experimental Section support the assignments made. The ir spectra of the 2-thio and 2-sulfonyl derivatives exhibited a carbonyl band at 1675–1680 cm^{-1} characteristic of a conjugated cyclohexenone.[3] The carbonyl band in 2-ethylsulfinylisophorone (**11**) appeared at 1650 cm^{-1}.

2-*p*-Toluenethioisophorone (**7**) was alternatively synthesized by reaction of sodium *p*-toluenethiolate with 2,3-isophorone oxide[4] (**9**) (Scheme II). Oxidation of **7** with *m*-chloroperbenzoic acid yielded **8**. Tomoeda and coworkers[5] have published the synthesis and nmr spectrum of 2-ethylthioisophorone (**10**) and therefore the preparation was repeated as shown in Scheme II for comparison of spectrum. The 2-ethylsulfinylisophorone (**11**) and 2-ethylsulfonylisophorone (**12**) were formed from **10** and the nmr spectra of these derivatives compared well with those of the corresponding *p*-tolyl analogs. Treatment of 4-bromoisophorone with sodium ethylthiolate gave isophorone and ethyl disulfide and no ethylthio-substituted isophorone (Scheme III), with displacement apparently occurring on the bromine and not on a carbon atom. Our work

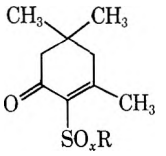
(1) J. N. Marx, A. W. Carnrick, and J. H. Cox, *J. Org. Chem.*, **37**, 2308 (1972).
(2) A. J. B. Edgar, S. H. Harper, and M. A. Kazi, *J. Chem. Soc.*, 1083 (1957).
(3) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 148.
(4) G. B. Payne *J. Org. Chem.*, **24**, 719 (1959).
(5) M. Tomoeda, M. Inuzuka, T. Furuta, M. Shinozuka, and T. Takahashi, *Tetrahedron*, **24**, 959 (1968).

SCHEME II



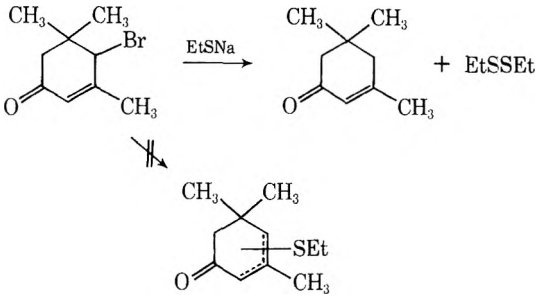
9

7, R = p-$CH_3C_6H_4$
10, R = CH_3CH_2



8, x = 2; R = p-$CH_3C_6H_4$
11, x = 1; R = CH_3CH_2
12, x = 2; R = CH_3CH_2

SCHEME III



supports the observations made by Marx, Carnrick, Cox[1] suggesting that nucleophilic reactions on 4-bromoisophorone take place in an SN2′ fashion with formation of 2-substituted derivatives and not in an SN2 reaction as earlier proposed.[2]

Experimental Section[6]

Preparation of 2-p-Toluenethioisophorone (7). Method A.—In 50 ml of EtOH was dissolved 2.3 g (0.10 mol) of sodium metal and to the solution was added 13.8 g (0.10 mol) of 90% p-toluenethiol. The sodium thiolate solution was then added to a solution of 21.7 g (0.10 mol) of 4-bromoisophorone dissolved in 100 ml of EtOH. After stirring for 5 hr, the precipitated NaBr was filtered and the filtrate was diluted with 100 ml of H_2O and extracted with CH_2Cl_2. The organic layer was reduced *in vacuo*, leaving 26 g of product, an oily liquid. A portion of the product was purified by distillation: bp 140–142° (0.07 mm); nmr ($CDCl_3$) δ 1.03 (s, 6, 5-$(CH_3)_2$–), 2.25 (s, 3, 3-CH_3), 2.25 (s, 3, $CH_3C_6H_4$–), 2.38 (s, 2, 6-CH_2–), 2.45 (s, 2, 4-CH_2–), 7.05 (s, 4, aromatic). This material was oxidized as given below to 2-p-toluenesulfonylisophorone (8).

Method B.—In 200 ml of EtOH was dissolved 10.1 g (0.44 mol) of sodium metal. To the solution was added 61 g (0.44 mol) of 90% p-toluenethiol and then 17 g (0.11 mol) of 2,3-isophorone oxide.[4] The solution was stirred for 12 hr and then diluted with 500 ml of H_2O. Extraction with CH_2Cl_2 and washing with H_2O and 0.1 N NaOH afforded 29 g of product upon removal of solvent *in vacuo*. A portion of the product was distilled, bp 142–144° (0.05 mm).

Anal. Calcd for $C_{16}H_{20}OS$: C, 73.80; H, 7.74; S, 12.32. Found: C, 73.48; H, 7.81; S, 12.34.

This material was shown by ir and nmr to be identical with that prepared by method A.

(6) All melting points are uncorrected. Infrared spectra data were obtained on a Perkin-Elmer Infracord spectrophotometer as Nujol mulls or neat. All nmr spectra were obtained on a Varian A-60 spectrometer in deuteriochloroform using TMS as the internal standard. Elemental analyses were obtained from the Analytical Services Laboratory of The Dow Chemical Co.

Preparation of 2-p-Toluenesulfonylisophorone (8). Method A.—To 10.8 g (0.05 mol) of 4-bromoisophorone[2] dissolved in 50 ml of DMF was added 8.9 g (0.05 mol) of sodium p-toluenesulfinate. The mixture was heated on a steam bath for 13 hr with precipitation of NaBr. The reaction mixture was then diluted with 200 ml of H_2O and extracted with CH_2Cl_2. The organic layer was washed with H_2O and reduced *in vacuo*, leaving 9.5 g (65% yield) of product which was recrystallized (EtOH): mp 147–149°; nmr ($CDCl_3$) δ 0.93 (s, 6, 5-$(CH_3)_2$–), 2.18 (s, 2, 6-CH_2–), 2.37 (s, 3, 3-CH_3), 2.52 (s, 2, 4-CH_2–), 2.58 (s, 3, CH_3-C_6H_4–), 7.25 and 7.83 (m, 4, J = 8.0 Hz, aromatic).

Anal. Calcd for $C_{16}H_{20}O_3S$: C, 65.72; H, 6.89; S, 10.97. Found: C, 65.46; H, 6.89; S, 11.18.

Method B.—To 18.8 g (0.072 mol) of 2-p-toluenethioisophorone prepared *via* displacement of sodium p-toluenethiolate as shown above dissolved in 140 ml of $CHCl_3$ was added 30.4 g (0.15 mol) of 85% m-chloroperbenzoic acid dissolved in 350 ml of $CHCl_3$. The reaction mixture was stirred for 4 hr and then washed with saturated $NaHCO_3$. The solvent was removed *in vacuo*, leaving 22 g (quantitative yield) of product which was recrystallized from acetone, mp 146–149°. This material was shown by ir and nmr to be identical with that synthesized by method A.

Preparation of 2-Ethylthioisophorone (10).—In 250 ml of EtOH was dissolved 16.5 g (0.72 mol) of sodium metal. To the solution was added 46.5 g (0.75 mol) of ethanethiol and then 28 g (0.18 mol) of 2,3-isophorone oxide.[4] After stirring for 12 hr, the reaction mixture was diluted with 500 ml of H_2O and extracted with CH_2Cl_2. The organic layer was reduced *in vacuo*, leaving 36 g (quantitative yield) of product which was purified by distillation: bp 128–131° (4.0 mm); lit.[5] mp 34–37.5°; nmr ($CDCl_3$) δ 1.03 (s, 6, 5-$(CH_3)_2$–), 1.15 (t, 3, CH_3CH_2S–), 2.24 (s, 2, 4-CH_2–), 2.25 (s, 3, 3-CH_3–), 2.37 (s, 2, 6-CH_2–), 2.72 (q, 2, CH_3CH_2S–).

Preparation of 2-Ethylsulfinylisophorone (11).—To 10 g (0.050 mol) of 2-ethylthioisophorone dissolved in 50 ml of glacial AcOH was added 5.72 g (0.051 mol) of 30% hydrogen peroxide. The mixture was stirred for 3 weeks at room temperature and then extracted with CH_2Cl_2. The organic layer was washed with 10% Na_2CO_3 and reduced *in vacuo*, leaving the product which was recrystallized (cyclohexane): mp 72.5–75°; nmr ($CDCl_3$) δ 1.05 (s, 6, 5-$(CH_3)_2$–), 1.28 (t, 3, CH_3CH_2SO–), 2.33 (s, 2, 6-CH_2–), 2.37 (s, 3, 3-CH_3–), 2.42 (s, 2, 4-CH_2–), 3.13 (q, 2, CH_3CH_2SO–).

Anal. Calcd for $C_{11}H_{18}O_2S$: C, 61.64; H, 8.47; S, 14.96. Found: C, 61.53; H, 8.56; S, 15.40.

Preparation of 2-Ethylsulfonylisophorone (12).—To 10 g (0.050 mol) of 2-ethylthioisophorone dissolved in 50 ml of glacial AcOH was added 11.5 g (0.10 mol) of 30% hydrogen peroxide. After stirring for 16 days, the reaction mixture was worked up by adding 200 ml of H_2O and extracting with CH_2Cl_2. The CH_2Cl_2 layer was washed with saturated Na_2CO_3 and reduced *in vacuo*, leaving 10.7 g (92% yield) of product which was recrystallized (cyclohexane): mp 71–73°; nmr ($CDCl_3$) δ 1.07 (s, 6, 5-$(CH_3)_2$–), 1.27 (t, 3, $CH_3CH_2SO_2$–), 2.38 (s, 2, 6-CH_2–), 2.48 (s, 3, 3-CH_3–), 2.55 (s, 2, 4-CH_2–), 3.38 (q, 2, $CH_3CH_2SO_2$–).

Anal. Calcd for $C_{11}H_{18}O_3S$: C, 57.36; H, 7.88, S, 13.92. Found: C, 57.36; H, 7.50; S, 14.21.

Registry No.—1, 16004-91-4; 7, 40919-40-2; 8, 40919-41-3; 9, 10276-21-8; 10, 17304-83-5; 11, 40919-43-5; 12, 40919-44-6; p-toluenethiol, 106-45-6; sodium p-toluenesulfinate, 824-79-3; sodium p-toluenethiolate, 10486-08-5; ethanethiol, 75-08-1.

Preparation and Photochemistry of Hexamethyl-2,5-cyclohexadienone Epoxides

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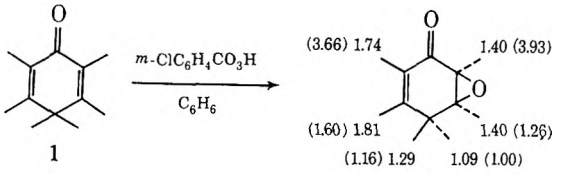
Received May 3, 1973

"The reaction of α,β-unsaturated ketones with peracids usually does not lead to epoxidation of the double

bond." [1] Instead, the carbonyl group is usually attacked. Although exceptions to this generality are known,[2] they are not common. We wish to report that the title dienone **1**[3] is readily epoxidized with *m*-chloroperbenzoic acid, whereas it is recovered unchanged from the usual alkaline peroxide[4] or peroxide–tungstate[5] treatments. We also describe the photoisomerization of the resulting epoxy ketone.

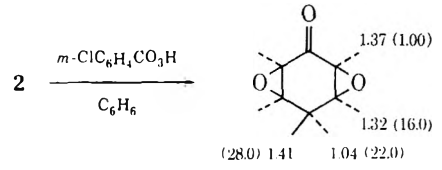
Treatment of **1** with *m*-chloroperbenzoic acid in benzene afforded the monoepoxide **2**. Its structure is



1 2

based on spectral data and further chemical transformations. The ir and uv spectra of **2** are consistent for an α,β-unsaturated cyclohexenone. The nmr spectrum[6] (see structure) is also reasonable. Epoxide prepared from **1** in which the C-3 and C-5 methyls were replaced by CD_3 groups[3] lacked the peak at δ 1.81, and the peak at δ 1.40 integrated for only three protons. Assuming that shift reagent coordinates at the carbonyl group but preferentially at the epoxide "face," the methyl group at δ 1.29 ,which has the larger europium shift and occurs at lowest field, is assigned as cis to the epoxide ring.

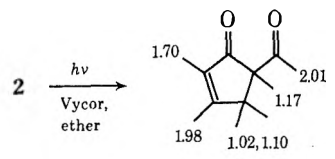
Further treatment of **2** with *m*-chloroperbenzoic acid gave the *cis*-diepoxide **3**. The crude reaction product



3

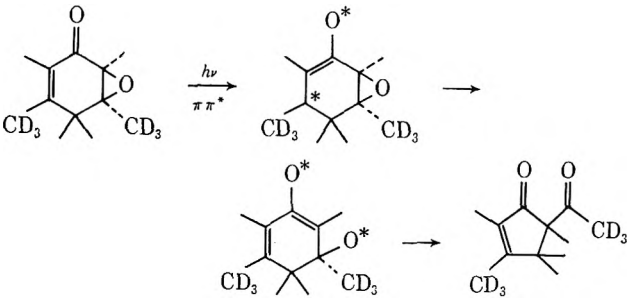
contained no nmr peaks in addition to those observed for pure **3**; thus there is no evidence for the presence of the trans isomer. The nmr spectrum,[6] which shows two different three-proton singlets for the *gem*-dimethyl group, requires the cis geometry. Diepoxide prepared from **1** in which the C-3 and C-5 methyls were replaced by CD_3 groups[3] lacked the singlet at δ 1.32. The europium shift data for **3** are curious in that coordination appears to occur remote from the carbonyl group.

Irradiation of **2** through a Vycor filter gave a single photoisomer, formulated as **4**. Ir, uv, and nmr data

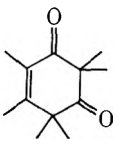


4

were consistent with the cyclopentenone and β-diketone moieties. When **4** was obtained from **2** labeled with CD_3 groups at C-3 and C-5, the nmr signals at δ 1.98 and 2.01 were absent. This is consistent with the following mechanism.



Ring contraction in the final step, rather than methyl migration to give **5**, is consistent with earlier results



5

on the irradiation of α,β-epoxy ketones.[7] Irradiation of **2** through Pyrex, in ether or acetone solution, caused no photoreaction, suggesting that the observed photoisomerization proceeds *via* $\pi\pi^*$ singlet excitation. It is interesting that the mass spectra of **2** and **4** are nearly identical, suggesting that a similar rearrangement may occur on electron impact.

Irradiation of **3** under a variety of conditions led only to recovered starting material.

Experimental Section

2,3-Epoxy-2,3,4,4,5,6-hexamethyl-2,5-cyclohexadienone (2).—A solution of 1.98 g (0.013 mol) of *m*-chloroperbenzoic acid in 50 ml of benzene was cooled to 0°. To this solution was added, slowly, a solution of 1.78 g (0.010 mol) of 2,3,4,4,5,6-hexamethyl-2,5-cyclohexadienone (**1**) in 10 ml of benzene. The mixture was stirred at 5° for 1 hr, then at room temperature for 14 hr. The benzene solution was washed successively with dilute sodium carbonate and saturated sodium chloride and dried ($MgSO_4$). Removal of the solvent (rotary evaporator) left a white residue (1.84 g) which was chromatographed over alumina (80–200 mesh) with benzene–carbon tetrachloride eluent (1:10). The first fraction was the desired monoepoxide **2**, 1.30 g (69%), mp 48–48.5°. The second fraction was unconverted dienone; no diepoxide **3** was formed under these conditions. The monoepoxide **2** had the following properties: ir (CCl_4) 1700 (w), 1655 (s), 1625 (m), 1470 (m), 1380 (s), 1365 (m), 1345 (m), 1280 (w), 1240 (w), 1205 (w), 1135 (m), 1105 (s), 1075 (m), 1025 (m), 1000 (w), 965 (w), 940 (m), 865 (s), 690 cm^{-1} (m); uv (cyclohexane) 323 nm (ϵ 86), 246 (8330); mass spectrum (70 eV) *m/e* (rel intensity)[8] 194 (3), 179 (8), 178 (4), 164 (4), 163 (6), 152 (100), 137 (86), 123 (34), 109 (12), 81 (45); nmr, see structure. *Anal.*[9] Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.93; H, 9.29.

***cis*-2,3:5,6-Diepoxy-2,3,4,4,5,6-hexamethyl-2,5-cyclohexadienone (3).**—To a cooled (ice) solution of 1.92 g (0.01 mol) of *m*-chloroperbenzoic acid in 30 ml of benzene was added slowly a solution of the monoepoxide **2** (0.97 g, 0.005 mol) in 10 ml of benzene. The mixture was allowed to warm to room temperature and stirred for 18 hr. The benzene solution was washed with dilute sodium carbonate and saturated sodium chloride, and dried ($MgSO_4$). Evaporation of the solvent and recrystalliza-

(1) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 306.

(2) Flavoindogenides (α-arylidene flavones) are an example: D. D. Keane, W. I. O'Sullivan, E. M. Philbin, R. M. Simons, and P. C. Teague, *Tetrahedron*, **26**, 2533 (1970).

(3) H. Hart and D. W. Swatton, *J. Amer. Chem. Soc.*, **89**, 1874 (1967).

(4) R. L. Wasson and H. O. House, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 522.

(5) G. B. Payne and P. H. Williams, *J. Org. Chem.*, **24**, 54 (1959).

(6) Determined in CCl_4 with TMS as internal reference; chemical shifts are in δ units, and values in parentheses are the relative slopes of the chemical shift differences as a consequence of adding the shift reagent Eu(fod)$_3$.

(7) C. S. Markos and W. H. Reusch, *J. Amer. Chem. Soc.*, **89**, 3363 (1967); for a review, see A. Padwa, *Org. Photochem.*, **1**, 91 (1967).

(8) Determined on a Hitachi Perkin-Elmer RMU-6 instrument.

(9) Spang Microanalytical Laboratory, Ann Arbor, Mich.

tion of the residue from hexane or methanol afforded 0.97 g (93%) of the diepoxide **3**, mp 80–81°. The same product could be obtained directly from **1** using an excess (two to threefold) of oxidant. Mixtures of **2** and **3** are difficult to resolve by column chromatography, though they can be separated by gas chromatography (10 ft × 0.25 in. column, 20% DEGS on 60/80 Chromosorb W, 150°): ir (CCl_4) 1685 (s), 1660 (w), 1630 (w), 1475 (m), 1455 (w), 1415 (m), 1380 (m), 1375 (w), 1340 (w), 1290 (w), 1255 (s), 1220 (w), 1165 (w), 1155 (w), 1120 (s), 1070 (m), 1030 (m), 940 (w), 875 (s), 700 cm^{-1} (m); uv (cyclohexane) 240 nm (ϵ 607), 217 (1960); mass spectrum (70 eV) *m/e* (rel intensity) 210 (2), 195 (3), 194 (0.5), 178 (4), 167 (20), 153 (32), 139 (100), 125 (37), 121 (33), 97 (43), 81 (49), 69 (40), 57 (46), 55 (91), 53 (64); nmr, see structure.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.39; H, 8.59.

Irradiation of 2.—A solution of 0.6 g of **2** in 30 ml of anhydrous ether was irradiated through Vycor with a 450-W Hanovia lamp. The photolysis was followed by vpc using a 5 ft × 0.25 in. column, 20% SE-30 on 60/80 Chromosorb W, 144°, He carrier gas flow 150 ml/min. As the reaction proceeded, the peak with a retention time of 9.5 min (starting material) decreased in area and a product peak appeared at 7.5 min. After 10 hr the reaction was complete and the product, **5-acetyl-2,3,4,4,5-pentamethyl-2-cyclopentenone** (**4**) was collected by preparative vpc: ir (CCl_4) 1690 and 1700 (broad, s) 1647 (m), 1385 (m), 1355 (m), 1325 (m), 1020 cm^{-1} (m); uv (cyclohexane) 233 nm (ϵ 14,750); mass spectrum (70 eV) *m/e* (rel intensity) 194 (20), 179 (3), 152 (100), 137 (90), 123 (19), 109 (33), 81 (24); nmr, see structure.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.23; H, 9.33.

Irradiation of ether or acetone solutions of **2** as above but through Pyrex gave only unchanged starting material.

Irradiation of 3.—Irradiation of a 1% solution of **3** in ether through quartz, or in acetone through Pyrex for 9–16 hr with a 450-W Hanovia lamp, gave only unchanged starting material.

Acknowledgment.—We are indebted to the National Science Foundation and the National Institutes of Health for financial support of this research.

Registry No.—**1**, 14790-04-6; **2**, 40940-60-1; **3**, 40940-61-2; **4**, 40940-46-3.

Photochemical Reactions of Nucleic Acid Constituents. Peroxide-Initiated Reactions of Purines with Alcohols

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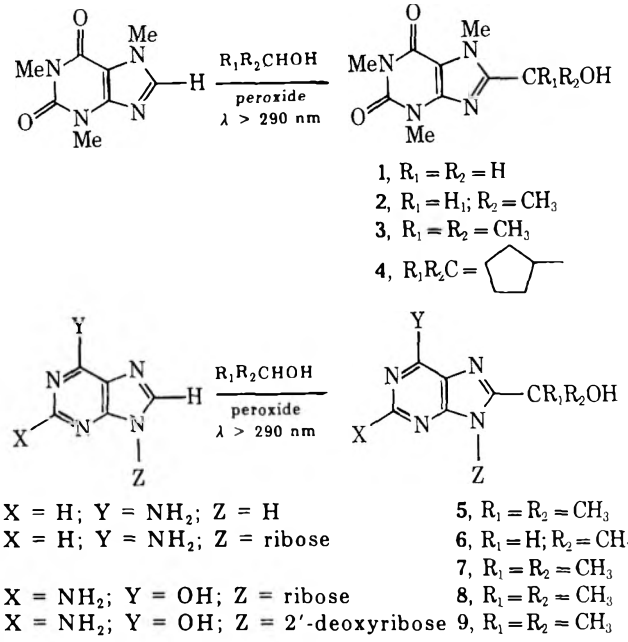
Received March 20, 1973

The photoalkylation of purines with alcohols has been described in recent years.[2] Most of these reactions led to the substitution of a hydroxyalkyl group for the C-8 hydrogen atom in the purine nucleus. The reactions were initiated either directly by ultraviolet light ($\lambda > 260$ nm), or through photosensitization with acetone ($\lambda > 290$ nm). We now report the light-induced reactions of purines with alcohols initiated with peroxides which lead to nearly quantitative yields of the appropriate C-8 hydroxyalkyl purines (with quantum yields of up to 0.05). A variety of peroxides, such as di-*tert*-butyl peroxide (DBP) and dicumyl peroxide (DCP), were employed in these reactions, all leading to high yields of the purine alcohol photoproduct. Light of $\lambda > 290$ nm or sunlight was used for the initiation of these reactions, which can be summarized as shown in Scheme I.

SCHEME I



The photoproducts were generally isolated by column chromatography and characterized through their physical properties, as well as by comparison with authentic samples.[2c,e] In some cases (*e.g.*, adenosine and 2-propanol), chromatography could be omitted in the work-up procedure, and the photoproduct was obtained by direct crystallization from the bulk of the reaction mixture. The reactions studied and the photoproducts isolated are summarized in Table I.

Traces ($\leq 1\%$) of 8-alkylpurines, the alkyl side chain of which depended on the alcohol employed, were sometimes found as by-products of the reactions. For example, 8-isopropyladenine was detected in the reaction of adenine with 2-propanol. A product (**10**)[2e] resulting from the alkylation both at the C-8 position and at the N-7 methyl group of caffeine could be isolated in minute amounts ($\leq 1\%$) from the caffeine–2-propanol reaction (see Experimental Section).

Spectral measurements indicated that most of the incident light is absorbed by the peroxide (*ca.* 90% with DBP). It is, therefore, suggested that the initiation of the reaction results from the light-induced fragmentation of the peroxide into free radicals, which abstract a hydrogen atom from the solvent, thus generating alcohol free radicals. The latter are scavenged by a purine molecule to yield, subsequently, the appropriate photoproduct.[2e]

To conclude, the reported reactions present a simple method for the synthesis of 8-hydroxyalkyl purines in high yields. The broad choice of alcohols in these reactions makes our method very versatile

(1) In partial fulfillment of the requirements for a Ph.D. thesis to be submitted to the Feinberg Graduate School.

(2) (a) H. Linschitz and J. S. Connolly, *J. Amer. Chem. Soc.*, **90**, 297 (1968); (b) D. Elad, I. Rosenthal, and H. Steinmaus, *Chem. Commun.*, 305 (1969); (c) H. Steinmaus, I. Rosenthal, and D. Elad, *J. Amer. Chem. Soc.*, **91**, 4921 (1969); (d) B. Evans and R. Wolfenden, *ibid.*, **92**, 4751 (1970); (e) H. Steinmaus, I. Rosenthal, and D. Elad, *J. Org. Chem.*, **36**, 3594 (1971); (f) Y. Yawazoa, M. Maeda, and K. Nushi, *Chem. Pharm. Bull.*, **20**, 1341 (1972).

TABLE I
PHOTOCHEMICAL REACTIONS OF PURINES WITH ALCOHOLS[a]

Purine	Registry no.	Alcohol	Registry no.	Photoinitiator	Product (yield, %)[b]
Caffeine	58-08-2	Methanol	67-56-1	DBP[c]	1 (90)
				DCP[d]	1 (97)
		Ethanol	64-17-5	DBP	2 (90)
				DCP	2 (86)
				DBP	2 (80)[e]
		2-Propanol	67-63-0	DBP	3 (87)
				DCP	3 (92)
				BHP[f]	3 (76)
				CHP[g]	3 (80)
				DBP	3 (90)[e]
				DCP	3 (85)[e]
		Cyclopentanol	96-41-3	DBP	4 (83)
Adenine	73-24-5	2-Propanol		DBP	5 (96)
				DCP	5 (100)
				BHP	5 (82)
				DBP	5 (85)[e]
				DCP	5 (82)[e]
Adenosine	58-61-7	Ethanol		DBP	6 (91)
				DCP	6 (100)
		2-Propanol		DBP	7 (100)
				DCP	7 (100)
				CHP	7 (86)
				DBP	7 (81)[e]
				DCP	7 (76)[e]
Guanosine	118-00-3	2-Propanol		DBP	8 (90)
				DCP	8 (90)
2′-Deoxyguanosine	961-07-9	2-Propanol		DBP	9 (90)
				DCP	9 (91)

[a] Hanovia 450-W high-pressure mercury vapor lamps (Pyrex filters) were used as the light source. [b] Yields are based on reacted purines. Conversions ranged from 80 to 100%. Irradiation time 22 hr. [c] Di-*tert*-butyl peroxide. [d] Dicumyl peroxide. [e] In sunlight (15–21 days). [f] *tert*-Butyl hydroproxide. [g] Cumyl hydroperoxide.

for the production of new purine derivatives, which may be of pharmacological significance.

Experimental Section

Caffeine (Schuchardt, Muenchen) was freshly crystallized from water prior to use. Other purines (Fluka, CHR grade) were used without purification. Alcohols were freshly distilled before irradiation. Petroleum ether refers to the fraction of bp 60–80°. Kieselgel, 0.063–0.20 mm (Merck, Darmstadt), was used for column chromatography (1 kg packed into a glass column 4.7 cm diameter × 1.20 m). Progress of the reactions was followed by ascending tlc on aluminum plates (Kieselgel SI F, Riedel-de-Haan), using acetone–petroleum ether mixtures for the caffeine derivatives and methanol–chloroform for other purines. Spots were detected by a Mineralight lamp. Chromatography was performed by using the "dry-column" technique[3] with properly deactivated silica gel, followed by elution with the appropriate solvent mixture. Irradiations were carried out in a Pyrex immersion apparatus, using Hanovia 450 W high pressure mercury vapor lamps, which were cooled internally with running water. The irradiation vessel was flushed for 15 min by oxygen-free nitrogen prior to irradiation, and nitrogen bubbling, as well as mechanical stirring, were sustained throughout the irradiation. Quantum yields were measured by ferrioxalate actinometry.[4] Nmr spectra were measured with a Varian A-60 instrument, using TMS as an internal standard. Absorptions are reported in τ values. Mass spectra were recorded on a MAT Atlas CH_4 instrument. Typical experiments are described. All other experiments were conducted under similar conditions.

Reaction of Caffeine and 2-Propanol (with DBP).—A mixture of caffeine (5 g), DBP (10 ml), 2-propanol (140 ml), and water (35 ml) was irradiated for 22 hr. Excess reagents were removed under reduced pressure, and the solid residue was chromatographed on silica gel (1 kg). Elution with acetone–petroleum ether (1:8) afforded pure **10**[2e] (0.03 g). Further elution with the same solvent mixture (1:6) gave **3** (5.1 g), followed by unreacted caffeine (0.54 g), which was eluted with a 1:4 mixture.

Reaction of Adenine and 2-Propanol (with DBP).—A mixture of adenine (2 g), DBP (8 ml), 2-propanol (135 ml), and water (40 ml) was irradiated for 22 hr. Excess reagents were removed under reduced pressure, and the solid residue was chromatographed on silica gel (500 g). Methanol–chloroform (1:10) eluted **5** (2.66 g), followed by unreacted adenine (0.1 g), which was eluted with a 1:8 mixture.

The reaction of caffeine and cyclopentanol yielded **4**, which exhibited mp 178–179° (from acetone–petroleum ether); nmr ($CDCl_3$) τ 5.88 (s, 3 H, $-N$-7-CH_3), 6.26 (broad s, 1 H, OH), 6.60 (s, 3 H, $-N$-3-CH_3), 6.68 (s, 3 H, $-N$-1-CH_3), and 7.95 [broad m, 8 H, $(CH_2)_4$].

Anal. Calcd for $C_{13}H_{18}N_4O_3$: C, 56.1; H, 6.5; N, 20.1; mol wt, 279. Found: C, 56.2; H, 6.7; N, 19.6; mol wt, 279 (mass spectrum).

Reaction of Caffeine and 2-Propanol (with Sunlight).—A mixture of caffeine (0.5 g), 2-propanol (140 ml), DBP (6 ml), and water (35 ml) was exposed to sunlight for 15 days (December). The usual work-up and chromatography led to **3** (0.53 g) and to recovered caffeine (0.05 g).

Reaction of Caffeine and 2-Propanol (with Visible Light).—A mixture of caffeine (0.05 g), 2-propanol (30 ml), DCP (2 g), and water (3 ml) was irradiated with 4 × 20 W fluorescent lamps (G. E.) for 285 hr, using a GWV filter (transmitting light of $\lambda > 370$ nm). The usual work-up and chromatography led to **3** (0.011 g) and to recovered caffeine (0.041 g). Other experiments using visible light led to the same photoproducts as those obtained with uv light. Conversions ranged from 20 to 45%. Irradiation time ranged from 150 to 300 hr.

(3) B. Loev and H. Goodman, *Intra-Sci. Chem. Rep.*, **4**, 283 (1970).
(4) C. A. Parker, *Proc. Roy. Soc., Ser. A*, **220**, 104 (1953).

Registry No.—**4**, 40919-45-7.

Vapor-Phase Thermolysis of Cyclic Malonyl Peroxides

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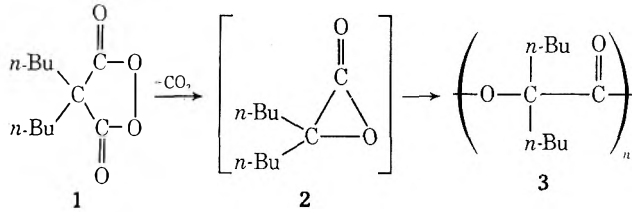
Received January 10, 1973

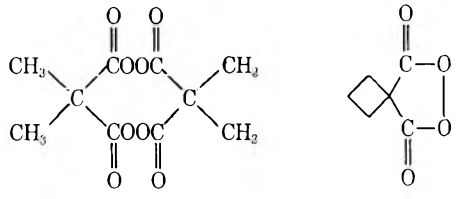
Recently Adam[1] has described an extensive study of the reactions of various peroxidic heterocycles, including cyclic malonyl peroxides. The major product of thermolysis or photolysis[2] of di(*n*-butyl)malonyl peroxide (**1**) in inert solvents is the polyester **3**. To



1 **2** **3**

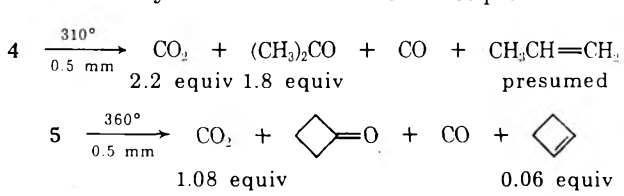
account for this product the authors postulated the formation of the intermediate α-lactone **2**. Subsequently, α-lactonic intermediates were detected directly by photolysis of neat malonyl peroxide matrices at 77°K.[3]

In this note we wish to report the products of vapor-phase thermolysis of the dimeric dimethylmalonyl peroxide (**4**) and monomeric trimethylenemalonyl peroxide (**5**). The major products from both **4** and **5** are



4 **5**

carbon dioxide and a ketone, acetone from **4** and cyclobutanone from **5**. Carbon monoxide was detected qualitatively. These three products are readily accounted for by the formation and subsequent decar-



bonylation of an α-lactonic intermediate. Decarbonylation has previously been reported to be a primary photochemical reaction of α-lactones.[3]

The small amount of cyclobutene produced from **5** probably arises from a carbene intermediate derived from the decarboxylation of the α-lactone or from some intermediate leading to it. Adam and Rucktäschel also observed low yields of olefins from the liquid-phase photochemical decomposition of **1**.[2] Although propene, the olefin anticipated from **4**, was not actually detected, the yields of carbon dioxide and acetone suggest that approximately 10% of the α-lactone decomposed by loss of another unit of carbon dioxide. This process would generate dimethylcarbene, which would be expected to rearrange to propene.

Mass spectra suggest that the radical ions produced by electron-impact ionization of **4** and **5** may follow fragmentation sequences rather similar to the vapor-phase thermolysis. There are prominent signals at *m/e* values appropriate for species isomeric with the α-lactone (loss of CO_2), the ketone (loss of CO_2 and CO), and the alkene (loss of $2CO_2$), in addition to peaks due to CO_2 and CO. There is also a prominent signal corresponding to a species formed by loss of CO_2 plus O from the monomeric molecular ion, for which no analogous thermolysis product (a ketene) was detected. Finally, it is interesting to note that no molecular ion was detectable in the mass spectrum of **4**. The highest signal appears at *m/e* 130, the molecular weight of the monomeric cyclic peroxide. This suggests that the molecular ion of **4** is unstable and rapidly fragments by the process shown below. It is also pos-

$$\underset{m/e\ 260}{[C_{10}H_{12}O_8]\cdot^+} \longrightarrow \underset{m/e\ 130}{[C_5H_6O_4]\cdot^+} + C_5H_6O_4$$

sible that some of the signals observed in the mass spectra are due to ions formed from molecular species generated in thermal processes occurring in the inlet, although significant thermal decomposition seems rather unlikely considering the low inlet temperature (50–60°).

Experimental Section

Caution.—Although we experienced no problems in handling any of the materials described in this note, we urge that all of these peroxidic compounds, the 90% hydrogen peroxide in particular, be treated as potentially hazardous substances.

Dimethylmalonyl Peroxide (**4**).—To a chilled solution of 2.14 g (0.0165 mol) of dimethylmalonic acid in 10 g of sulfuric acid was added 2.2 ml of 90% hydrogen peroxide over 50–60 min. After 2 ml of cold saturated ammonium sulfate solution was added, the mixture was filtered and the solid was washed twice with 5-ml portions of cold saturated ammonium sulfate solution, dissolved in ether, and dried with magnesium sulfate. Removal of the ether and sublimation (0.1 mm, room temperature) gave 1.4 g (64%) of product: mp 48–49°; nmr ($CDCl_3$) τ 8.4 (sharp singlet); mass spectrum (25 eV, inlet temperature 60°) *m/e* (rel intensity) 130 (43), 86 (24), 70 (base peak), 58 (12), 44 (36), 42 (92), 28 (10); ir ($CHCl_3$) $\nu_{C=O}$ 1820 and 1804 cm^{-1} (shoulder). The ratio of intensities of the absorptions of 1820 and 1804 cm^{-1} was variable. Whether this was a consequence of some conformational equilibrium involving the peroxide, or was merely an artifact due to some minor impurity, was not established.

Anal. Calcd for $C_{10}H_{12}O_8$: C, 46.15; H, 4.61; active O, 12.31; mol wt, 260. Found: C, 46.28; H, 4.68; active O (titrimetric), 12.05; mol wt, 259 (ebullioscopic, methanol), 263 (Rast, camphene).

Trimethylenemalonyl Peroxide (**5**).[3]—This peroxide was synthesized in 56% yield by the same procedure described above: mp 63–64°; nmr ($CDCl_3$) τ 7.38 (broad, complex multiplet); mass spectrum (25 eV, inlet temperature 50°) *m/e* (rel intensity) 142 (50), 98 (20), 82 (64), 70 (29), 54 (73), 44 (base peak), 28 (64); ir ($CHCl_3$) $\nu_{C=O}$ 1803 cm^{-1}.

Anal. Calcd for $C_6H_6O_4$: C, 50.70; H, 4.23; active O, 11.26; mol wt, 142. Found: C, 50.81; H, 4.17; active O (titrimetric), 11.12; mol wt, 143 (ebullioscopic, $CHCl_3$).

Vapor-Phase Thermolysis.—A sample of the peroxide was sublimed through a 10 in. tube maintained at 310° for 4 and 360° for **5**, while a pressure in the apparatus of 0.4–0.5 mm was maintained. The flask from which the peroxide was sublimed

(1) W. Adam, presented at the symposium on the Chemistry of Heterocyclic Compounds, Gordon Research Conference, New Hampton, N. H., June 30, 1972.

(2) W. Adam and R. Rucktäschel, *J. Amer. Chem. Soc.*, **93**, 557 (1971).

(3) O. L. Chapman, P. W. Wojtkowski, W. Adam, O. Rodriquez, and R. Rucktäschel, *J. Amer. Chem. Soc.*, **94**, 1365 (1972).

was held at a temperature no higher than 26°. The effluent from the tube was passed through two traps, the first cooled in a Dry Ice–acetone bath, the second in liquid nitrogen. At the end of a pyrolytic run there was no residue in the flask from which the peroxide was sublimed, in the pyrolysis tube, or in areas of the apparatus which would experience intermediate temperatures, such as immediately preceding or following the pyrolysis tube. Thus there is no indication of the formation of any polyester analogous to **3** during vapor-phase pyrolysis.

Ketonic products were condensed in the Dry Ice–acetone bath. Acetone was identified by its retention time on glc, by coinjection with authentic acetone, and by conversion to its DNP derivative, mp 125–127° (lit.[4] mp 126°). The yield of acetone produced in the thermolysis was determined from the weight of DNP isolated. Cyclobutanone was identified by its retention time on glc, by coinjection with authentic cyclobutanone, and by conversion to its DNP derivative, mp 144–146° (lit.[4] mp 146°). Material collected in the Dry Ice–acetone trap exhibited no infrared absorption indicative of the presence of polyester analogous to **3**.

The yield of carbon dioxide was determined by venting the contents of the liquid nitrogen trap through a tube packed with Ascarite, and measuring the increase in weight.

Carbon monoxide was detected qualitatively be venting the contents of the liquid nitrogen trap through a solution of cuprous sulfate. An increase in weight signified the absorption of carbon monoxide.[5]

Cyclobutene was identified as a component of the contents of the liquid nitrogen trap by its retention time on glc, by coinjection with authentic cyclobutene, and by conversion to its Diels–Alder adduct with 1,3-diphenylisobenzofuran, mp 119–121°, identical with that of an authentic sample. The yield of cyclobutene was determined from the weight of the Diels–Alder adduct isolated.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work, and to the U. S. Army Research Office, Durham (DA-31-124-AROD-476).

Registry No.—**4**, 40982-37-4; **5**, 34867-87-3; dimethylmalonic acid, 595-46-0; trimethylenemalonic acid, 5445-51-2; hydrogen peroxide, 7722-84-1.

(4) Z. Rapporport, "Handbook of Tables for Organic Compound Identification," 3rd ed, Chemical Rubber Co., Cleveland, Ohio, 1967, p 161.

(5) A. E. Heron and H. N. Wilson in "Comprehensive Analytical Chemistry," Vol. 1A, C. L. Wilson and O. W. Wilson, Ed., Elsevier, New York, N. Y., 1959, p 243.

Kinetics of the One-Electron Transfer Reaction of Trimethyl Phosphite with Quinones[1]

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Received February 27, 1973

The reaction of trialkyl phosphite with quinones is well known.[3] For example, the reaction of *o*-quinones such as phenanthrenequinone and *o*-benzoquinone gives 1:1 adducts at room temperature,[4] while acenaphthenequinone gives a 2:1 adduct, which was produced by a rapid reaction of the 1:1 adduct with the second quinone molecule.[5,6] The reaction of *p*-quinones with trivalent phosphorus compounds yields reduction products of quinones, *e.g.*, *p*-alkoxyphenols *via* quinone–donor adducts.[7,8] The electron paramagnetic resonance spectrum was observed during the reaction of triethyl phosphite with chloranil,[9] but little is known about the detail of this phenomenon.

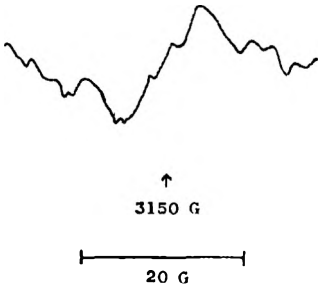


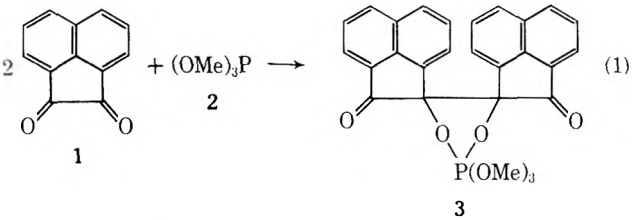
Figure 1.—Esr spectra obtained in the reaction of acenaphthenequinone with trimethyl phosphite in dioxane.

We have reported that the reaction of acenaphthenequinone with trimethyl phosphite caused the color change, the initiation of autoxidation of trimethyl phosphite, and polymerization of styrene,[10] which suggest the occurrence of radicals in the reaction. However, nothing is known on the mechanism of this radical formation and the relative amount of the radical formation and the relative amount of the radical product to the ionic product (a 2:1 adduct).

The present paper will describe further evidence and kinetics of the radical formation *via* one-electron transfer from phosphite to quinones to clarify its mechanism and the ratio of the radical to ionic paths. The paper will also describe the relation between the rate and the reduction potentials of some quinones.

Results and Discussion

As reported previously, the reaction of acenaphthenequinone (**1**) with excess trimethyl phosphite (**2**) at 25° under N_2 gave a 2:1 adduct of **1** and **2** [2,2,2-trimethoxy-4,5-biacenedionoxy-1,3,2-dioxaphospholane (**3**)] on the basis of its nmr and ir spectra.



The reaction mixture of acenaphthenequinone (**1**) and trimethyl phosphite (**2**) showed a red color shift. The color of DPPH vanished on addition of the reaction mixture, and the red color of the complex also disappeared. These observation suggest the presence of radicals.[10] On mixing **1** and **2** in dioxane, an esr signal was observed as shown in Figure 1. The rapid mea-

(1) Contribution No. 194.

(2) To whom correspondence should be addressed.

(3) (a) R. F. Hudson, "Structure and Mechanism in Organo-Phosphorus Chemistry," Academic Press, London, 1965, p 187; (b) F. Ramirez, *Accounts Chem. Res.*, **1**, 168 (1968).

(4) F. Ramirez and N. B. Desai, *J. Amer. Chem. Soc.*, **85**, 3252 (1963).

(5) (a) F. Ramirez and N. Ramanathan, *J. Org. Chem.*, **26**, 3041 (1961); (b) F. Ramirez, S. B. Bhatia, and C. P. Smith, *J. Amer. Chem. Soc.*, **89**, 3030 (1967).

(6) F. Ramirez, H. J. Kugler, and C. P. Smith, *Tetrahedron*, **24**, 1931 (1968).

(7) (a) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **23**, 778 (1958); (b) F. Ramirez and S. Dershowitz, *J. Amer. Chem. Soc.*, **81** 587 (1959); (c) F. Ramirez, E. H. Chen, and S. Dershowitz, *ibid.*, **81**, 4338 (1959).

(8) F. Ramirez and S. Dershowitz, *J. Amer. Chem. Soc.*, **78**, 5614 (1956).

(9) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 856 (1957).

(10) Y. Ogata and M. Yamashita, *Bull. Chem. Soc. Jap.*, **46**, 2208 (1973).

TABLE I
RATE CONSTANTS FOR THE REACTION OF QUINONES WITH TRIMETHYL PHOSPHITE

Quinone	Initial concn, M: [Quinone]$_0$	Initial concn, M: [P(OMe)$_3$]$_0$	$10^2 k$, M^{-1} sec^{-1}	Solvent	Temp, °C
Acenaphthenequinone	0.0170	0.329	1.99	Dioxane	30.0
	0.0170	0.165	1.96	Dioxane	30.0
	0.00850	0.329	1.90	Dioxane	30.0
	0.00425	0.165	2.01	Dioxane	30.0
	0.00697	0.152	6.78	Acetonitrile	21.0
5,6-Dinitroacenaphthenequinone	0.00544	0.394	1.12×10^{-2}	Dioxane	30.0
	0.00544	0.197	1.12×10^{-2}	Dioxane	30.0
	0.00272	0.394	1.13×10^{-2}	Dioxane	30.0

surement of uv spectra of the reaction mixture in dioxane showed λ_{max} 550 nm. The authentic acenaphthenesemiquinone radical produced by the treatment of acenaphthenequinone with metallic sodium showed λ_{max} 570 nm, which is similar to the results obtained by Evans, *et al.*[11] These results suggest the formation of acenaphthenesemiquinone radical (**4**) and trimethyl phosphite radical cation (**5**).

The kinetic study of reaction of quinones with trimethyl phosphite was carried out spectrophotometrically in dioxane or acetonitrile at 20–30°. The rate law is first order in each of two substances (eq 2). The kinetic data are shown in Table I; the data fit eq 2.

$$v = -\mathrm{d[quinone]}/dt = k[\mathrm{quinone}][2] \quad (2)$$

The rate constant has a good constancy up to 90% conversion. The rate law and the data in Table I show that the first rearrangement step of phosphorus atom from carbonyl carbon atom to carbonyl oxygen atom may be rate determining.[12]

The rate of one-electron transfer reaction was followed by means of spectrophotometry of disappearing DPPH in dioxane under air or nitrogen atmosphere. No color change of DPPH was observed in the absence of either phosphite or quinone. The rate was independent of quinone and DPPH concentrations, as shown in Table II. The data in the table fit eq 3 except for the case in the absence of quinones.

$$v' = -\mathrm{d[DPPH]}/dt = k'[2]^{0.4} \quad (3)$$

TABLE II
RATE OF DISAPPEARANCE OF DPPH IN THE REACTION OF ACENAPHTHENEQUINONE WITH TRIMETHYL PHOSPHITE IN DIOXANE

Initial concn, M: 10^3·[Quinone]$_0$	Initial concn, M: 10^2·[P(OMe)$_3$]$_0$	Initial concn, M: 10^3·[DPPH]$_0$	Temp, °C	Atmosphere	Rate constant,[a] $10^5 k'$, $10^{0.6}$ sec^{-1}
7.87	7.50	2.54	30.0	Air	1.63
3.94	7.50	2.54	30.0	Air	1.63
7.87	3.75	2.54	30.0	Air	1.64
7.87	7.50	1.27	30.0	Air	1.64
7.87	15.4	2.54	30.0	Air	1.67
0	7.50	2.54	30.0	Air	0
7.90	8.77	0.149	25.0	Air	0.826
7.86	8.77	0.149	20.0	Air	0.415
8.04	8.67	0.149	30.0	N_2	1.66

[a] $v = -\mathrm{d[DPPH]}/dt = k'[2]^{0.4}$.

No appreciable effect of oxygen on the rate was observed. Temperature effect on the rate constant at 20–30° afforded the values of energy and entropy of activation of 22 kcal/mol and −15 eu (at 25.0°), respectively. Electron-attracting substituents on quinones facilitate the electron transfer, as shown in Table III.

The reaction of chloranil with trimethyl phosphite with an induction period of *ca.* 2.5 min had a larger rate constant than that of acenaphthenequinone, which had no induction period. Virtually no decolorization of DPPH was observed with anthraquinone. DPPH is known to react in some cases with nonradical species, *e.g.*, a hydrogen atom is abstracted from anthracene,[13] but the observed no reaction of DPPH with phosphite or quinones implies that DPPH reacts with the radicals[14] produced by the reaction of phosphite with quinones.

The observed induction period for the decolorization of DPPH in the case of chloranil (**8**) and no decolorization in the absence of quinones seem to suggest the initial formation of a quinone–phosphite complex, *e.g.*, probably a charge-transfer complex, which is liable to give radical species and acts as a catalyst.

The order of 0.4 in phosphite is close to 0.5. The order of 0.5 seems to suggest that two radical species [Me· and ·P(O)(OMe)$_2$] may be produced from **5** (Scheme I, path a), whose rate law is expressed as eq 4.

$$v = -\mathrm{d[DPPH]}/dt = k_r[\mathrm{radicals}][\mathrm{DPPH}] = k_a'[2]^{0.5} \quad (4)$$

Alternatively, the order is explicable assuming that other radical species [MeO· and Me·] are produced from **5** (path b), whose rate law is represented by eq 5.

$$v = -\mathrm{d[DPPH]}/dt = k_r'[\mathrm{radicals}][\mathrm{DPPH}] = k_b'[2]^{0.5} \quad (5)$$

However, there seems as yet to be no evidence to decide among paths a and b in view of the available literature.[15] Another mechanisms involving a simple one-electron transfer from phosphite to quinone followed by a chain reaction can be excluded from the observed rate law (eq 3).

The comparison of the consumption rate of **1** and DPPH in Tables I and II shows that the ionic reaction to produce an acenaphthenequinone–trimethyl phosphite (2:1) adduct (**3**) is much more important by a factor of 10^2–10^4 than the one-electron transfer reaction to produce radical ions.

(11) A. G. Evans, J. C. Evans, and E. H. Godden, *J. Chem. Soc. B*, 546 (1969).
(12) Y. Ogata and M. Yamashita, *Tetrahedron*, **27**, 2725 (1971).
(13) J. S. Hogg, D. H. Lohmann, and K. E. Russell, *Can. J. Chem.*, **39**, 1394 (1961).
(14) C. E. H. Bawn and S. F. Mellish, *Trans. Faraday Soc.*, **47**, 1216 (1951).
(15) (a) J.-J. L. Fu and W. G. Bentrude, *J. Amer. Chem. Soc.*, **94**, 7710 (1972); (b) J.-J. L. Fu, W. G. Bentrude, and C. E. Griffin, *ibid.*, **94**, 7717 (1972).

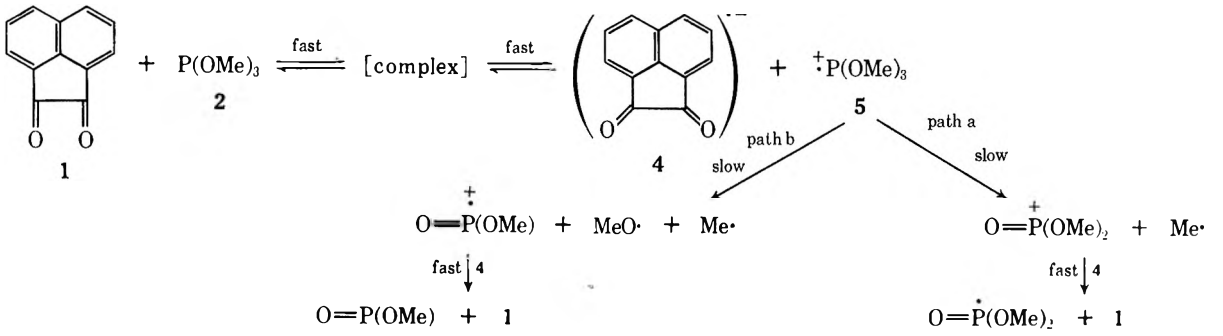
TABLE III

RATE OF DISAPPEARANCE OF DPPH IN THE REACTION OF VARIOUS QUINONES WITH TRIMETHYL PHOSPHITE IN DIOXANE AT 30.0°

Quinones	Initial concn, M: 10^3[Quinone]$_0$	10^3[P(OMe)$_3$]$_0$	10^4[DPPH]$_0$	Rate constant $10^6 k'$, $M^{0.6}$ sec^{-1}	Reduction potential, V
5,6-Dinitroacenaphthenequinone (6)	4.33	1.59	1.49	5.96	
5-Nitroacenaphthenequinone (7)	4.67	1.59	1.49	4.75	
Chloranil (8)	4.93	7.93	1.49	4.30[a]	0.712[b]
Acenaphthenequinone (1)	7.87	7.50	12.7	1.64	0.78
p-Benzoquinone (9)	4.67	507	1.49	0.312	0.698[c]
Phenanthrenequinone (10)	6.07	507	1.49	7.30×10^{-4}	0.458[d]
Anthraquinone (11)	6.57	507	1.49	Too slow to measure	0.157[e]

[a] Rate constant after induction period. [b] K. Wallenfels and W. Möhle, *Ber.*, **76**, 924 (1943). [c] J. B. Conant and L. F. Fieser, *J. Amer. Chem. Soc.*, **44**, 2480 (1922). [d] L. F. Fieser, *ibid.*, **51**, 3101 (1929). [e] J. B. Conant and L. F. Fieser, *ibid.*, **46**, 1855 (1924).

SCHEME I



The rate of one-electron transfer reaction seems to correlate with the reduction potential of quinones; *i.e.*, a plot of log k' *vs.* reduction potential fits well a straight line, whose slope is 12. This shows that the energy barrier for this reaction correlates with the reduction potential of quinone (Table III). The substitution by a nitro group seems to afford a little higher reduction potential to acenaphthenequinone.[16]

Experimental Section

Materials.—Trimethyl phosphite [bp 58° (116 mm)], acenaphthenequinone (mp 261°), chloranil (mp 299°), phenanthrenequinone (mp 210°), *p*-benzoquinone [mp 115.5° (lit.[17] mp 115.7°)], anthraquinone [mp 286–287° (lit.[18] mp 286°)], 5-nitroacenaphthenequinone [mp 210° (lit.[19] mp 218°)], and 5,6-dinitroacenaphthenequinone [mp > 300° (lit.[19] mp >300°)] were used.

Product.—The reaction of 1 with excess 2 was carried out at 25° under N_2. After distillation of unreacted 2 *in vacuo*, the product was analyzed by nmr ($CDCl_3$), τ 1.5–2.5 (multiplet, 12 H), 6.28 (doublet, J_{PH} = 10.6 Hz, 9 H). The yield of 3 was almost quantitative.

Kinetics.—The disappearance of color of DPPH [$\lambda_{max}^{dioxane}$ 515 nm (ϵ 5310)] was followed by means of spectrophotometry. Each 1-ml portion of dioxane solution of 1, 2, and DPPH was introduced separately into a three-necked quartz uv cell. After air was substituted by N_2, the three solutions were mixed and the cell was placed in a thermostated cell chamber of an Hitachi EPU-2A spectrophotometer. The consumption of DPPH was determined spectrophotometrically at appropriate intervals of time.

On the other hand, the disappearance of color of 1 [$\lambda_{max}^{dioxane}$ 473 nm (ϵ 17.9)] was followed by almost the same procedure as above.

Esr Spectra.—Esr spectra were observed by mixing a dioxane solution of trimethyl phosphite and acenaphthenequinone in an esr tube at the temperature of the melting point of dioxane. Field and modulation width were 3150 ± 100 and 20 G, respectively.

Reduction Potential.—The reduction potential of quinones was measured in 50% aqueous ethanol containing 0.1 *N* HCl as a 10^{-4}–10^{-3} *M* solution of substrate at 20° by a Yanagimoto P8-DPR polarograph potentiostated with a calomel electrode.

Registry No.—1, 82-86-0; 2, 121-45-9; 3, 40782-66-9; 6, 27471-02-9; 7, 24040-42-4; 8, 2435-53-2; 9, 106-51-4; 10, 84-11-7; 11, 84-65-1.

(16) L. F. Fieser, *J. Amer. Chem. Soc.*, **51**, 3101 (1929).
(17) J. M. Robertson, *Proc. Roy. Soc., Ser. A*, **150**, 106 (1935).
(18) (a) R. Kempf, *J. Prakt. Chem.*, [2] **78**, 257 (1908); (b) H. R. Snyder and F. X. Werber, *J. Amer. Chem. Soc.*, **72**, 2965 (1950).
(19) F. Rowe and J. S. Herbert, *J. Chem. Soc.*, **117**, 1344 (1920).

Conversion of o-Acylphenylacetic Acids to Naphthalene and Chrysene Derivatives[1]

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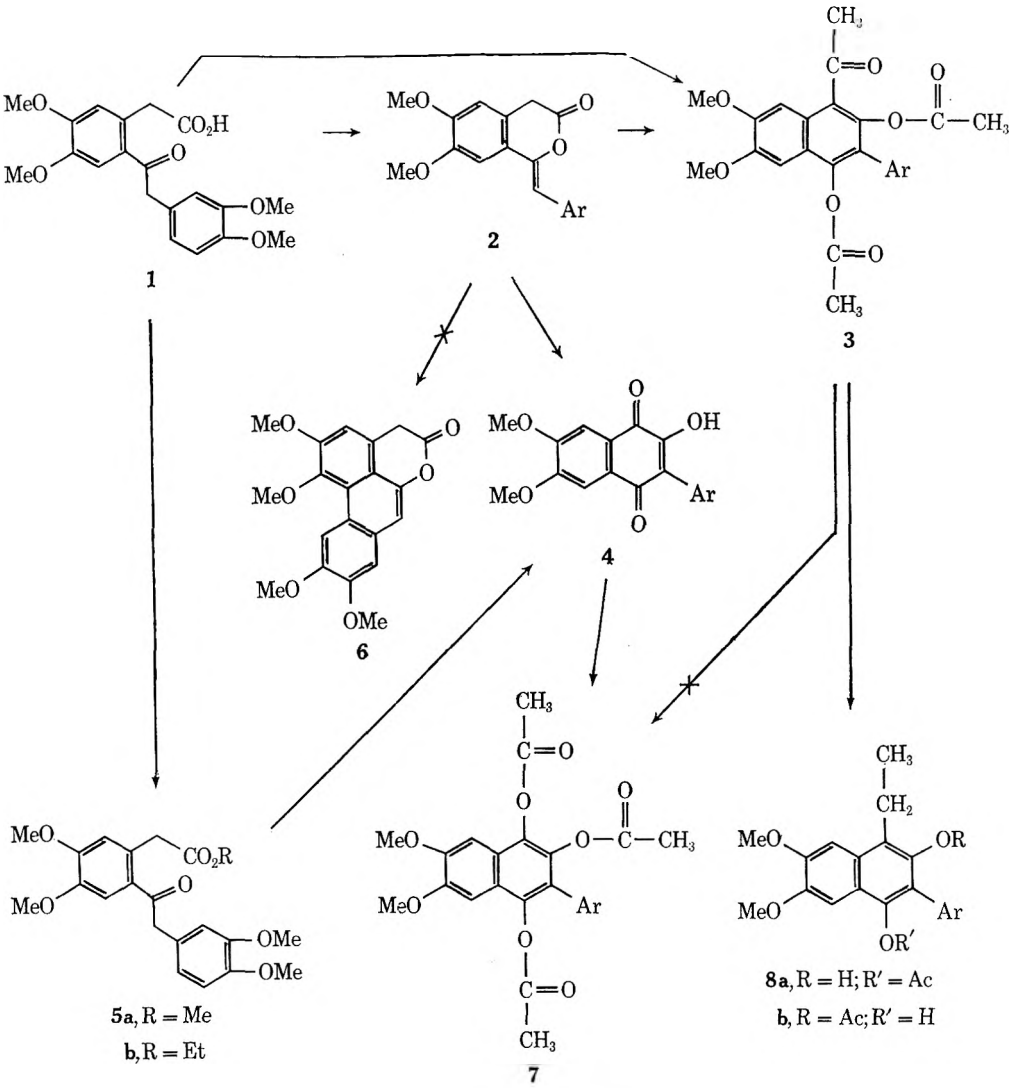
Received March 13, 1973

2-[(3,4-Dimethoxyphenylacetyl)-4,5-dimethoxyphenyl]acetic acid (1) has been used in a new total synthesis of 1-benzylisoquinoline alkaloids, and one of key intermed ates in that work was 1-(3,4-dimethoxybenzylidene)-6,7-dimethoxy-3-isochromanone (2) obtained by thermal dehydration of 1.[2] The present work was undertaken in an effort to find a milder reaction to convert 1 to 2, and in the initial attempts the keto acid 1 was heated for 1 hr in a solution of acetic anhydride in pyridine. The purified product, obtained in about 52% yield, was identified as 1-acetyl-2,4-diacetoxy-3-(3,4-dimethoxyphenyl)-6,7-dimethoxynaphthalene (3). The structure proof of 3 rested on the elemental analysis and on the uv, ir, nmr, and mass spectra (see Experimental Section) as well as on the chemical conversion to the known 1,4-naphthoquinone derivative 4.

(1) This study was supported in part by a grant from the National Science Foundation (GY 6169).
(2) I. W. Elliott, Jr., *J. Heterocycl. Chem.*, **9**, 853 (1972).

SCHEME I



Ar = 3,4-dimethoxyphenyl

In subsequent reactions we have found that heating **1** in pyridine–acetic anhydride for a shorter period resulted in the formation of a mixture of **3** and the isochromanone **2**. From a reaction of **1** in acetic anhydride alone, the substituted 3-isochromanone **2** was isolated in moderate yield, but compound **3** was not detected under these conditions. Moreover, when **2** was subjected to treatment with hot pyridine and acetic anhydride it was converted to the naphthalene derivative **3**. These results suggest that **2** is a possible intermediate in the cyclization of **1** to **3**; these transformations are outlined in Scheme I.

Both **2** and **3** are readily oxidized by alcoholic sodium hydroxide and air to the 1,4-naphthoquinone derivative **4**. Compound **4** has been prepared earlier from the keto ester **5**,[3,4] and its structure was established by Bentley. The formation of **4** from **3** requires the loss of the 1-acetyl group from the aromatic ring by carbon–carbon bond cleavage; although there are reports for loss of aryl and alkoxy groups from 4-substituted 1,2-naphthoquinones under mild conditions to give the 2-hydroxy-1,4-naphthoquinone system,[5] probably the nearest analogy for the oxidation of **3** to **4** is the transformation of the keto ester **5** to **4** in which Bentley and coworkers offered evidence that an intermediate 1,3-dihydroxynaphthalene was oxidized by air to the 1,4-naphthoquinone **4**.

The same 1,4-naphthoquinone **4** was also prepared from **2** by an oxidative photochemical reaction of **2**. The photochemical reaction was originally undertaken in an attempt to couple the two benzene rings in **2** to synthesize a tetracyclic oxygen analog (**6**) of certain of the aporphine alkaloids. Under the conditions used none of compound **6** has been obtained.

Two additional reactions of **3** were tried, based on known functional group reactions. Although a triacetoxynaphthalene compound (**7**) was readily prepared by reductive acetylation of **4** using zinc and acetic anhydride, we were not able to oxidize the naphthyl ketone **3** to **7** under Baeyer–Villiger conditions. The reaction of sodium borohydride with **3** did not lead to the anticipated carbinol; rather the product of this mild reduction is assigned the structure **8** for the several

(3) H. R. Bentley, W. Dawson, and F. S. Spring, *J. Chem. Soc.*, 1763 (1952).

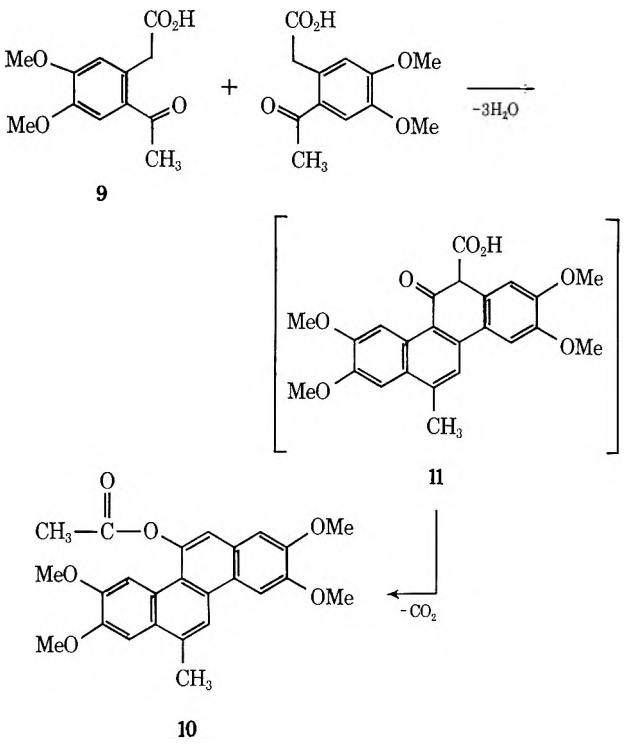
(4) I. W. Elliott, *J. Heterocycl. Chem.*, **7**, 1229 (1970).

(5) S. C. Hooker and J. G. Walsh, Jr., *J. Chem. Soc.*, **65**, 321 (1894); L. F. Fieser, *J. Amer. Chem. Soc.*, **48**, 2922 (1926).

following reasons: (1) the elemental analysis fit a formula $C_{24}H_{26}O_7$ but not $C_{26}H_{28}O_9$; (2) the mass spectrum shows a peak for the parent ion at *m/e* 426; (3) the nmr spectrum clearly shows the pattern of an ethyl group, in addition to one acetyl and an OH group. Either **8a** or **8b** fits this description, and since this compound was peripheral to our investigation we have made no detailed study of it. However, the reduction by borohydride of a carbonyl group to the methylene stage[6] and facile hydrolysis of one specific ester linkage suggest a proximity effect that would favor the formation of **8a** over **8b**.

By contrast with the *o*-(phenylacetyl)phenylacetic acid (**1**), when 6-acetyl-3,4-dimethoxyphenylacetic acid (6-acetylhomoveratric acid) was heated in pyridine–acetic anhydride solution, the major compound isolated proved to be 11-acetoxy-6-methyl-2,3,8,9-tetramethoxychrysene. The elemental analysis and spectral data support the constitution **10** for this product, and its formation from 2 mol of 6-acetylhomoveratric acid (**9**) can be rationalized by Scheme II. An intermediate

SCHEME II



such as **11**, with a β-keto acid unit, provides an explanation for the ready decarboxylation required in the final formulation of the chrysene derivative **10**. The examples whereby 2-hydroxy-1-naphthoic acid[7] and to a lesser extent 1-hydroxy-2-naphthoic acid[8] are decarboxylated in boiling water serve as models for the chrysene case. The sketchy trend in ease of decarboxylation from salicylic acid through the hydroxy naphthoic acids to the hypothetical chrysene intermediate **11** may parallel the greater relative importance of the keto tautomers in each of these compounds.

(6) Reductions have been reported of acetyl to ethyl groups in other substituted naphthalenes: R. E. Moore, H. Singh, C. W. J. Chang, and P. J. Scheuer, *J. Org. Chem.*, **31**, 3638 (1966); H. Singh, T. L. Folk, and P. J. Scheuer, *Tetrahedron*, **25**, 5301 (1969). We thank one of the referees for calling this work to our attention.

(7) G. Kaufmann, *Ber.*, **15**, 804 (1882).

(8) R. Schmitt and E. Burkard, *Ber.*, **20**, 2699 (1887).

Experimental Section

1-Acetyl-2,4-diacetoxy-3-(3,4-dimethoxyphenyl)-6,7-dimethoxynaphthalene (3). A. From the Keto Acid.—The keto acid (**1**, 2 g) in pyridine (12 ml) and acetic anhydride (10 ml) was heated to boiling for 10 min and allowed to stand for 18 hr. The solution was stirred into aqueous 10% HCl (150 ml), and the solid which separated was collected and immediately recrystallized from EtOH. The solution deposited 1.5 g (52%) of pale golden crystals: mp 200–201°; *m/e* 482 (M^+); uv λ_{max}^{EtOH} 247 nm (log ε 4.75), 289 sh (4.08), 337 (3.07); ir (paraffin oil mull) 1760, 1690 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.99, 2.15, 2.70 (each 3 H, s, $COCH_3$), 4.00 (12 H, m, 4 OCH_3), 6.99–7.40 (5 H, m).

Anal. Calcd for $C_{26}H_{26}O_9$: C, 64.74; H, 5.43. Found: C, 64.47; H, 5.44.

B. From 1-(3,4-Dimethoxybenzylidene)-6,7-dimethoxy-3-isochromanone (2).—The lactone **2** (2 g) in pyridine (15 ml) and acetic anhydride (10 ml) was allowed to reflux for 30 min and to stand for 20 hr. When the solution was added to 10% HCl solution (150 ml) a solid was obtained. Recrystallization from EtOH gave a golden crystalline product (1.2 g), mp 200–201°. An infrared spectral comparison showed that this product was identical with compound **3** in part A.

2-(3,4-Dimethoxyphenyl)-3-hydroxy-6,7-dimethoxy-1,4-naphthoquinone (4). A. From the Keto Ester 5b.—To a mixture of the keto acid (1.5 g) in absolute EtOH (150 ml) was added ethyl chloroformate (10 ml). The mixture was warmed for 10 min and allowed to stand overnight. The ester **5b** (4.8 g) separated on cooling and was recrystallized from EtOH as a colorless solid, mp 106–107°.

Anal. Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found: C, 65.84; H, 6.56.

The ester **5b** (2 g) was suspended in EtOH (50 ml) and treated with 20% sodium hydroxide solution (20 ml). A deep purple color developed immediately and the solid gradually dissolved. After standing exposed to the air for 18 hr the solution was poured into 10% HCl solution (200 ml) and a red solid (2 g) was collected. The naphthoquinone **4** was recrystallized from a mixture of MeOH and $CHCl_3$ as orange needles, mp 230–231° (lit.[3] mp 226°).

B. From the Naphthyl Ketone 3.—A suspension of **3** (1 g) in EtOH (30 ml) was mixed with 20% NaOH solution (10 ml). The characteristic violet color (see part A) developed within 1 min but not so quickly as with the keto ester **5b**. Within 2 hr all of the solid has dissolved and the solution was dark purple. After 24 hr the reaction mixture was poured into 10% HCl (150 ml) and a red solid (1 g) precipitated. The naphthoquinone was recrystallized from $CHCl_3$–MeOH as orange crystals, mp 229–230°, that had an infrared spectrum identical with that of the product from part A.

C. From the Isochromanone 2 by Reaction with Base.—The isochromanone **2** (1 g) reacted with NaOH in EtOH in the same proportions as in part B, and within 3 min a purple color had developed. After 30 hr the naphthoquinone was isolated quantitatively from HCl solution and recrystallized from $CHCl_3$–MeOH as orange crystals, mp 230–231°, *m/e* 370 (M^+). The infrared spectrum showed that the product was identical with Bentley's naphthoquinone.[3]

Anal. Calcd for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90. Found: C, 65.08; H, 5.02.

D. From the Isochromanone 2 by Photolysis.—A solution of **2** in *t*-BuOH (200 ml)–C_6H_6 (60 ml) was irradiated with exposure to air for 24 hr in a Rayonet Model RPR-100 reactor equipped with 3000-Å lamps. Evaporation of the dark red solution gave a gum which was washed several times with petroleum ether (bp 30–60°) to leave a red solid (0.2 g), mp 222–223°. Recrystallization of the crude product from $CHCl_3$–MeOH gave orange crystals, mp 228–229°. The ir spectrum of this product was superimposable on that of Bentley's naphthoquinone (**4**).[3]

Sodium Borohydride Reduction of 3.—A suspension of the naphthyl ketone **3** (1 g) in EtOH (20 ml) was allowed to react with sodium borohydride (0.4 g). After 20 min at room temperature the mixture was boiled for 3 min and diluted with water (20 ml). Acetic acid was added dropwise until the evolution of gas ceased, and the mixture was diluted to 100 ml with water. After cooling, the supernatant liquid was decanted, and the solid was recrystallized from EtOH (15 ml)–THF (5 ml) as nearly colorless plates (0.35 g): mp 190–191°; *m/e* 426 (M^+); ir 3440 (OH) and 1760 cm^{-1} (ester C=O), there was no band at

1690 cm^{-1} that was assigned to the ketone C=O in the starting compound **3**; nmr δ 1.3 (3 H, t, CH_3 of Et), 2.1 (3 H, s, $COCH_3$), 3.1 (2 H, q, CH_2 of Et), 3.9 (12 H, m, 4 OCH_3), 5.0 (1 H, s, OH), 7.0–7.3 (5 H, m, ArH).

Anal. Calcd for $C_{24}H_{26}O_7$: C, 67.59; H, 6.15. Found: C, 67.70; H, 6.23.

1,3,4-Triacetoxy-2-(3,4-dimethoxyphenyl)-6,7-dimethoxynaphthalene (7).—Reductive acetylation of the naphthoquinone **4** with zinc dust in acetic anhydride after the procedure described by Bentley[4] gave the triacetyl derivative **7**, mp 221–222°.

Anal. Calcd for $C_{26}H_{26}O_{10}$: C, 62.65; H, 5.26. Found: C, 62.63; H, 5.42.

An attempt to prepare **7** by oxidation of **3** by *m*-chloroperbenzoic acid led to 60% recovery of **3** and *m*-chlorobenzoic acid (83%) but, there was no evidence for the formation of **7**.

6-Acetylhomoveratric Acid (9).—3,4-Dimethoxyphenylacetic acid (15 g, homoveratric acid) was dissolved in warm acetic acid (25 ml) and the solution was stirred into polyphosphoric acid (200 g). After standing at room temperature for 2 days with occasional stirring, the reaction mixture was added to water (1500 ml) and the aqueous solution was extracted continuously with ether (1300 ml) for 18 hr. Evaporation of the ether extract left 12 g of colorless solid that after recrystallization from water (3 parts)–EtOH (1 part) had mp 175–176° (lit.[3] mp 175°). The identification of the product was by comparison with a sample prepared by Bentley's method and by oxidation to the known 3,4-dimethoxyhomophthalic acid.[3] Compound **9** could also be isolated in several crops from the water solution on long standing (1–3 weeks).

11-Acetoxy-6-methyl-2,3,8,9-tetramethoxychrysene (10).—A mixture of 6-acetylhomoveratric acid (9, 2 g) in pyridine (16 ml) and acetic anhydride (12 ml) was heated under reflux conditions for 1 hr. After standing for 12 hr, the red solution was added to 300 ml of 10% HCl solution and the crude product (1.8 g, mp 120°) was collected. Extraction of the solid with hot MeOH left a residue (0.75 g), mp 253–258°. The chrysene derivative was purified by recrystallization from $CHCl_3$–petroleum ether: mp 263–265°; *m/e* 420 (M^+); ir 1750 cm^{-1} (C=O); uv λ_{max}^{EtOH} 231 nm (log ϵ 4.81), 259 sh (4.60), 279 sh (5.02), 287 (5.15), 307 (4.54), 319 (4.34), 334 (4.26), 362 (4.00), 380 (4.08); nmr δ 2.51 (3 H, s, CH_3), 2.75 (3 H, s, CH_3CO), 4.14 (12 H, m, OCH_3), 7.20–8.75 (6 H, m, ArH).

Anal. Calcd for $C_{28}H_{24}O_6$: C, 71.42; H, 5.75. Found: C, 71.09; H, 5.70.

Registry No.—1, 26954-85-8; 2 30034-55-0; 3, 40940-67-8; 4, 40940-48-5; 5b, 40940-49-6; 7, 40940-50-9; 8a, 40940-51-0; 9, 38210-84-3; 10, 40940-53-2; homoveratric acid, 93-40-3.

A Convenient Preparation of Tetrahydrofurylidene Acetates

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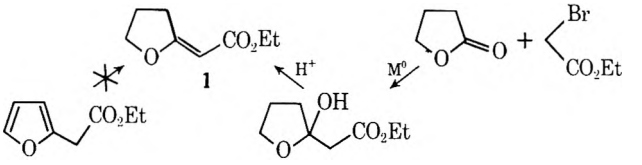
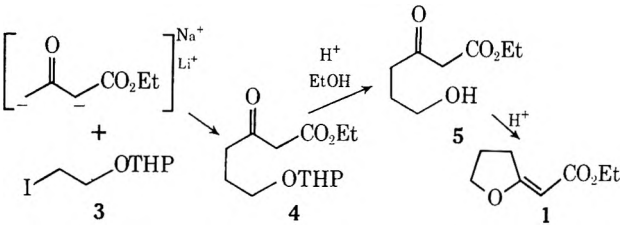
Received April 23, 1973

Recent heterocyclic studies have required reduced derivatives of furan for synthetic building blocks. This had led to a convenient preparation of ethyl α-(tetrahydro-2-furylidene)acetate (**1**) by a novel epoxide ring cleavage. The preparation of this compound (**1**) by the reduction of furan esters seemed unlikely. The reaction of organometallics with γ-butyrolactone proved to be a complex process but did, on treatment with acid, afford furylidene acetate **1** in 24% yield from γ-butyrolactone.[1] Use of the dianion of ethyl acetoacetate (**2**), following the procedure of Weiler,[2]

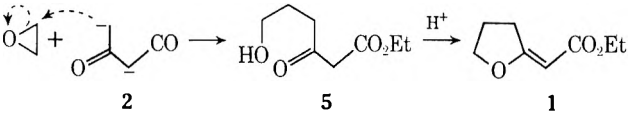


proved a very simple approach to the formation of the carbethoxymethylene tetrahydrofuran **1**.



Initially, the dianion of ethyl acetoacetate (**2**) was alkylated with the tetrahydropyranyl ether (THP) of iodoethanol (**3**), forming a new β-keto ester, **4**, alkylation occurring at the methyl rather than methylene position of ethyl acetoacetate. This was converted into **1** in 34% yield (from ethyl acetoacetate) by treatment with first aqueous ethanol and acid (**4** → **5**) and then benzene and *p*-toluenesulfonic acid (**5** → **1**). The same alkylation procedure with the THP of chloro- or bromoethanol failed to yield keto ester **4** in any usable quantities.

Improvement in the preparation of ester **1** was facilitated by the discovery that the dianion of ethyl acetoacetate (**2**) would undergo smooth epoxide ring opening[3] in a manner analogous to the above-cited alkylation reaction (bond formation occurring at the methyl position of ethyl acetoacetate). When approximately 1 equiv of ethylene oxide was added to litho sodio ethyl acetoacetate (**2**) a crude alcohol **5** was formed which was readily transformed into tetrahydrofuran **1** on treatment with oxalic acid in methylene chloride (54% yield). The generality of this novel dianion epoxide ring opening and enol etherification is apparent from the reduced furan and thiophene derivatives that have been prepared from **2** and are listed in Table I.[5]



The product of initial epoxide (sulfide) ring opening (*i.e.*, **5**) was never purified. However, the spectral data (ir, nmr) from these crude products, **5**, and the analogous compounds from propylene oxide and butylene oxide (propylene sulfide) suggest these alcohols (mercaptans) could be isolated and used for synthetic transformations other than simple intramolecular enol etherification.

The stereochemistry about the double bond of these esters is as shown in Table I (E or trans). This is apparent from shift reagent studies which confirm the close proximity of the ester carbonyl and allylic, methylene ring protons. That is, assuming proton deshielding decreases as the intramolecular distance

(1) F. F. Blick and B. A. Brown, *J. Org. Chem.*, **26**, 3685 (1961), and references cited therein.

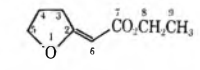
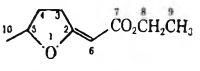
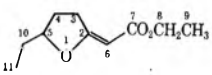
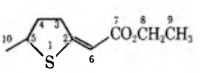
(2) L. Weiler, *J. Amer. Chem. Soc.*, **92**, 6707 (1970); L. Weiler, *Tetrahedron Lett.*, 4809 (1971).

(3) For examples of sodio ethyl acetoacetate epoxide ring opening see ref 4; to our knowledge this study represents the first report of a dianion epoxide ring cleavage.

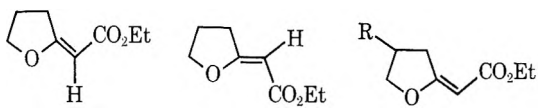
(4) A. Graham, A. Millidge, and D. Young, *J. Chem. Soc.*, 2180 (1954); T. Temnikova, G. Markina, V. Borodavko, and N. Yaskina, *Zh. Org. Khim.*, **6**, 739 (1970); G. El Naggar and B. Ershov, *ibid.*, **5**, 1368 (1969).

(5) All products were characterized by ir, nmr, uv, mass spectra and C, H analysis.

TABLE I

Product	Epoxide (sulfide) used	Bp, °C (0.5 mm)	Yield from ethyl acetoacetate, %
 1		55	54
 6		80	62
 7		100	60
 8		120	57

to the shift reagent increases and that this reagent coordinates on the ester carbonyl oxygen, it follows that isomer **1**, and not **9**, is the only geometrical isomer isolated in these reaction sequences.[6,7]



1 **9** 10, R = Me or Et

Unsymmetrical epoxides (sulfides) were employed in this study to ascertain the direction of ring opening. In the reactions attempted, the least hindered attack lead to the products (**6**, **7**, and **8**) isolated and shown in Table I. The isomeric enol ether **10** (above) has not been detected by glc, lc, nmr-shift reagent, or ^{13}C studies. However, the yields of **6**, **7**, and **8** do not preclude the formation of such isomeric compounds.

Shift reagents were again employed to clearly show the methine proton resonance (C_5, see Table I for numbering) in compounds **6** and **7** and the absence of any methylene proton resonances that would be observed if isomeric compound **10** (R = Me or Et) were present.[6] In addition, the ^{13}C-proton decoupled nmr of furylidene **6** exhibited single resonances for C_5 and C_8 at the chemical shift expected confirming the homogeneity of this sample.[8] Studies related to the reactivity of these systems are now underway.

Experimental Section

General Method.—The dianion of ethyl acetoacetate was prepared in THF using Weiler's procedure.[2] To this was added the epoxide or sulfide (1.1 equiv) at 0° and the reaction mixture was immediately brought to room temperature. After 3 hr, water (10 ml/10 mmol of dianion) was added, then dilute HCl (aqueous 5%) until the mixture was neutral to weakly basic. This was extracted with ether (three times), and the combined organic phases were washed with saturated, aqueous sodium bicarbonate and brine and dried over sodium sulfate. The volatiles were removed *in vacuo* and the residue was combined with an equal weight of oxalic acid in methylene chloride (50 ml/g of residue) and heated under reflux for 2 hr in an inert atmosphere. After cooling, this mixture was washed with water, sodium bicarbonate (saturated, aqueous), and brine (saturated, aqueous) and dried over sodium sulfate. The volatiles were removed *in vacuo;* the residue was distilled at reduced pressure. (Glc, 5-ft 10% SE-30, 155–175°, and lc, Lichrosorb, cyclohexane–THF elution, analyses were conducted on all carbethoxymethylene compounds.)

Ethyl α-(Tetrahydro-2-furylidene)acetate (1).—Ethylene oxide (~2.2 g, 0.05 mol) was added to the dianion of ethyl acetoacetate (0.05 mol) in the manner described above. This afforded 4.6 g of **1**: 54%; λ_{max}^{film} 1701, 1642 cm^{-1}; λ_{max}^{EtOH} 245 nm (ε 13,400); pmr in $\delta_{TMS}^{CCl_4}$ 5.06 (t, J = 0.4 Hz, 1, C-6 H), 4.08 (t, J = 7.0 Hz, 2, C-5 H's), 3.95 (q, J = 7.0 Hz, 2, $-O-CH_2-CH_3$), 3.00 (m, 2, C-3 H's), 2.01 (m, 2, C-4 H's), 1.18 (t, J = 7.0 Hz, 3, $-OCH_2CH_3$); 156 (*m/e*); bp 50° (0.05 mm); cmr in ppm_{TMS}^{neat} 176.6 (C_2, see Table I for numbering), 167.5 (C_7), 89.0 (C_6), 71.8 (C_5), 58.8 (C_8), 30.2 (C_3), 23.6 (C_4), 14.5 (C_9).

Anal. Calcd for $C_8H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.31; H, 7.11.

Ethyl α-(Tetrahydro-5-methyl-2-furylidene)acetate (6).—The dianion of ethyl acetoacetate (0.05 mol) and propylene oxide (2.91 g, 0.05 mol) afforded 5.27 g of **6**: 62%; λ_{max}^{film} 1701, 1645 cm^{-1}; λ_{max}^{EtOH} 245 nm (ε 13,400); pmr in $\delta_{TMS}^{CCl_4}$ 5.04 (t, J = 0.4 Hz, 1, C-6 H), 4.26 (m, 1, CH_3CHO-), 3.82 (q, J = 7.2 Hz, 2, $-OCH_2-CH_3$), 2.87 (m, 2, C-3 H's), 1.97 (m, 2, $-CHCH_2CH_2-$), 1.17 (d, J = 7.0 Hz, 3, C-5 H), 1.04 (t, J = 7.2 Hz, 3, $-OCH_2CH_3$); 170 (*m/e*); bp 80° (0.05 mm); cmr in ppm_{TMS}^{neat} 176.1 (C_2), 167.5 (C_7), 89.0 (C_6), 80.3 (C_5), 58.3 (C_9), 31.1 (C_3), 30.6 (C_4), 20.1 (C_8), 14.3 (C_{10}).

Anal. Calcd for $C_9H_{14}O_3$: C, 60.74; H, 8.92. Found. C, 60.79; H, 8.99.

Ethyl α-(Tetrahydro-5-ethyl-2-furylidene)acetate (7).—The dianion of ethyl acetoacetate (0.05 mol) with 1,2 butylene oxide (3.60 g, 0.05 mol) afforded 5.52 g of **7**: 60%; λ_{max}^{film} 1709, 1645 cm^{-1}; λ_{max}^{EtOH} 245 nm (ε 13,500); pmr $\delta_{TMS}^{CCl_4}$ 5.04 (t, J = 0.4 Hz, 1, C-6 H), 4.14 (m, 1, C-5 H), 3.97 (q, J = 7.4, 2, $-OCH_2CH_3$); 2.95 (m, 2, C-3 H's), 2.00–1.62 (m, 4, C-4 H's and C-10 H's), 1.21 (t, J = 7.0, 3, CH_3CH_2-), 1.10 (t, J = 7.4, 3, $-OCH_2CH_3$); 184 (*m/e*); bp 100° (0.05 mm).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.38; H, 8.72.

Ethyl α-(Tetrahydro-5-methyl-2-thiophenylidene)acetate (8).—The dianion of ethyl acetoacetate (0.048 mol) with propylene sulfide (3.56 g, 0.048 mol) afforded 5.20 g of **8**: 57%; λ_{max}^{film} 1709, 1645 cm^{-1}; λ_{max}^{EtOH} 288 (ε 13,500); pmr δ_{TMS}^{CCl} 5.70 (t, J = 0.4 Hz, 1, C-6 H), 4.06 (q, J = 7.0 Hz, 2, $-OCH_2CH_3$), 3.58 (m, 1, C-5 H), 2.81 (m, 2, C-3 H's), 2.18 (m, 2, $-CHCH_2CH_2-$), 1.37 (d, J = 6.5 Hz, 3, CCH_3), 7.23 (t, J = 7.0 Hz, 3, $-OCH_2CH_3$); 1.86 (*m/e*); bp 120° (0.05 mm).

Anal. Calcd for $C_9H_{14}O_2S$: C, 58.05; H, 7.58. Found: C, 58.17; H, 7.47.

Acknowledgments.—This work was supported by the American Cancer Society Grant No. IC-83.

Registry No.—**1**, 40954-14-1; **6**, 40954-15-2; **7**, 40954-16-3; **8**, 40954-17-4;e thylene oxide, 75-21-8; litho sodio ethyl acetoacetate dianion, 40902-62-3; propylene oxide, 75-56-9; 1,2-butylene oxide, 106-88-7; propylene sulfide, 1072-43-1.

(6) The shift reagent used was trisdipivalomethanatoeuropium(III) or Eu(DPM)$_3$.

(7) H. M. McConnell, R. E. Robertson, *J. Chem. Phys.*, **29**, 1361 (1958), and references cited therein.

(8) The predicted and observed ^{13}C chemical shift of compound **6** are within experimental error based on model acrylate and tetrahydrofuran systems, as well as the parent unsubstituted furylidene **1**.

The Orientation in Alkaline Halogenation of 2-Butanone

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Received May 22, 1973

In a recent communication[1] the products of reactions of 2-butanone (I) and its 1-bromo (II) and 3-bromo

(1) C. G. Swain and R. P. Dunlap, *J. Amer. Chem. Soc.*, **94**, 7204 (1972).

TABLE I

REACTIONS[a] OF 1- AND 3-SUBSTITUTED 2-BUTANONES IN AQUEOUS ALKALI AT 25°

Substituent	[Ketone]	[OH⁻]	[Bromine]	$k_{exp} \times 10^3$ sec^{-1}	$k \times 10^2$ M^{-1} sec^{-1}
1-Bromo (II)	<0.001	0.005[b]	0.0019	590	11,800
1-Hydroxy (IV)	0.0025	0.08	0.01	7.70	9.6
3-Bromo (III)	0.0025	0.08	0.01	13.6	17.9
3-Hydroxy (V)	0.0025	0.08	0.01	14.9	
1-Bromo (II)	0.0025	5.0×10^{-4}		76.5	3,060[c]
	0.005[d]	9.2×10^{-5}		3.00	3,260[e]
	0.005[f]	6.9×10^{-5}		2.17	3,150[e]
					Av 3,160[g]
3-Bromo (III)	0.005[h]	1.81×10^{-5}		2.39	13,200[e]
	0.005[i]	1.03×10^{-5}		1.25	12,200[e]
					Av 12,700[g]
H[j]	0.0025	0.1	0.0105	9.43	9.43

[a] Reactions with bromine were followed colorimetrically at 350 nm. Those with hydroxide ion alone were followed conductimetrically or by pH-Stat. All concentrations are in mol dm^{-3}. In each case the hydroxide concentration has been estimated with allowance for hydrolysis of bromine according to the equation $Br_2 + 2OH^- \rightleftharpoons Br^- + OBr^- + H_2O$. [b] An average value. [c] Hydroxide consumption was monitored conductimetrically; thus $k = k_{exp}/[ketone]$. [d] pH = 9.95, $\mu \simeq 1.5 \times 10^{-3}$, $\gamma = 0.97$. [e] Bromo ketone hydrolysis was monitored by pH-Stat titration; thus $k = k_{exp}/[OH^-]$. [f] pH = 9.82, $\mu \simeq 2.5 \times 10^{-3}$, $\gamma = 0.95$. [g] Second-order rate constant for hydroxide-promoted bromo ketone hydrolysis. [h] pH = 9.25, $\mu \simeq 8 \times 10^{-3}$, $\gamma = 0.92$. [i] pH = 9.00, $\mu \simeq 1.5 \times 10^{-3}$, $\gamma = 0.97$. [j] Reference 6.

(III) derivatives with aqueous NaOBr were reported. The results indicated clearly that, in the NaOH-induced bromination of I, in aqueous solution at 25°, each hydrogen on C-1 and C-3 is attacked equally fast to form the sodium enolate precursors of intermediates II and III which rapidly give mainly sodium propionate and sodium lactate, respectively, along with bromoform. These results are consistent with the traditional ketone halogenation mechanism and obviate the need for different rate-determining steps for alkaline halogenation and deuterium exchange.[2-4]

During a reexamination of the evidence for "Hal B I" and "Hal B II" ketone halogenation mechanisms,[2-4] we reached the following conclusions regarding the fate of II and III (under comparable halogenation conditions) by a study which is complementary to the product study outlined above.

The claim[5,6] that I halogenates much more rapidly at the 1 than at the 3 position is based entirely upon the low yields of α-halogenated propionic acids obtained among the products of reaction of I with NaOBr. We suspected, however, that hydroxide-induced nucleophilic displacement of Br^- from either II or III might compete with their multihalogenation and subsequent fragmentation by the haloform reaction.

For each bromo ketone we therefore determined the product of reaction with hydroxide ion and compared the rate of this reaction with that which occurs in the presence of bromine also.

Reaction of II and III with aqueous NaOH gave only the corresponding 1- and 3-hydroxy ketones (IV and V), respectively. The reactions were monitored by continuous conductivity measurement. Rates of bromine uptake by solutions of II and III in aqueous NaOBr were determined from the decrease with time of the intensity of absorption at 350 nm. Reactions were initiated by both stop-flow and conventional techniques where appropriate. The results are in Table I.

The rate of hydrolysis ($k_{OH^-} = 31.6$ M^{-1} sec^{-1}) of II is of the same order of magnitude as that determined for its bromination ($k = 118$ M^{-1} sec^{-1}) in aqueous hydroxide; thus it can be shown that the latter rate constant must actually represent the sum of the rate constants for the competing reactions ($k = k_{OH^-} + k_{Br_2}$) and therefore $k_{Br_2} = 86.4$ M^{-1} sec^{-1}. The much slower subsequent bromination of the minor product has been monitored and both the bromination rate constant and amount of bromine consumed (relative to the initial fast bromination) are consistent with the competitive formation of IV (27%) during the initial fast step.

The rate of bromination of IV was measured independently for comparison. The rate constants for bromination of II and IV, respectively, are 916 and 1.02 times as fast as that for the bromination of I. The former ratio is comparable with an 800-fold increase in the catalytic rate constant for hydroxide-induced deprotonation brought about by monochlorination of acetone[7] and accounts for the exclusive formation[1] of bromoform and propionic acid upon bromination of II in aqueous NaOBr.

It was, however, found that the *apparent* uptake of bromine by III in aqueous NaOBr is very slow in comparison with the rate of displacement of bromide ion and it is clear that the observed halogenation is that of V which is formed in an initial fast step. It was noted that 13.3% of the overall halogen consumption also occurred rapidly during this initial period and, by analogy with the discussion above, it can be argued that 3-bromo-2-butanone initially undergoes competitive hydrolysis (86.7%) and bromination (13.3%) under these conditions. Thus the bromination rate constant must equal *ca.* $(k_{OH^-} \times 13.3)/86.7 = 19.5$ M^{-1} sec^{-1}. An approximate estimate of the rate of the fast step gave $t_{1/2} = 1.3 \pm 0.2$ sec, $k_{exp} = 5.3 \pm 0.8$ sec^{-1} and $k = k_{OH^-} + k_{Br_2} = 133 \pm 20$ M^{-1} sec^{-1} which is consistent with this interpretation.

Since the rate of bromination is much slower than the rate of displacement of bromide ion, α-halogenated propionic acids are not the expected products of halogenative degradation of III in aqueous hydroxide. The ultimate products of reaction under these condi-

(2) C. Rappe, *Acta Chem. Scand.*, **20**, 1721 (1966).
(3) C. Rappe, *Acta Chem. Scand.*, **21**, 857, 1823 (1967).
(4) C. Rappe, *Acta Chem. Scand.*, **22**, 219 (1968).
(5) C. F. Cullis and M. H. Hashmi, *J. Chem. Soc.*, 2512 (1956); 1548 (1957).
(6) C. F. Cullis and M. H. Hashni, *J. Chem. Soc.*, 3080 (1957).
(7) R. P. Bell and A. Lidwell, *Proc. Roy. Soc., Ser. A*, **176**, 88 (1940).

tions will be those derived from V which we have found to brominate at a rate comparable with that of I.

The kinetic results support the failure of Swain and Dunlap[1] to detect appreciable deuterium incorporation in unreacted III under conditions where it had undergone 57% conversion to V in alkaline D_2O.

Experimental Section

Materials.—3-Bromo-2-butanone [n^{20}D 1.4575, bp 85° (118 mm)] and 1-bromo-2-butanone [n^{20}D 1.4676, bp 104° (118 mm)] were prepared by the procedure of Catch, *et al.*[8] Upon hydrolysis of the corresponding bromobutanones (5 g, 0.033 mol) in aqueous sodium hydroxide (100 ml, 2 *M*) at room temperature there was obtained 1-hydroxy-2-butanone (n^{20}D 1.4271, bp 158°) and 3-hydroxy-2-butanone (n^{20}D 1.4168, bp 144°), respectively, in high yield.

Kinetics.—Reactions of the bromobutanones with sodium hydroxide were initiated using a Durrum Gibson stop-flow apparatus fitted with a T-jump cell. The syringes contained bromo ketone (0.005 *M*) and sodium hydroxide (0.001 *M*), respectively. Reactions were followed by monitoring change in conductivity between the plates of the T-jump compartment.[9] A Radiometer automatic titration assembly was also used for an alternative pH-Stat procedure.

Reactions of 1- and 3-bromo- and of 1- and 3-hydroxy-2-butanone (0.005 *M*) with bromine (0.024 *M*) in aqueous hydroxide (0.1 *M*) were initiated by stop-flow techniques and followed by colorimetric observation of the change in absorbance at 398 nm. Stop-flow results were consistent with those obtained using a Gilford 2400 spectrometer to monitor (at 350 nm) consumption of BrO^- in a solution which initially contained hydroxide (0.01 *M*), bromine (0.003 *M*), and bromo ketone (<0.001 *M*).

Registry No.—I, 78-93-3; II, 816-40-0; III, 814-75-5; IV, 5077-67-8; V, 513-86-0.

(8) J. R. Catch, D. F. Elliott, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 272 (1948).

(9) Unpublished procedure: A. C. Knipe and R. L. Tranter.

Pyrolytic Cleavage of Antibiotic X-537A and Related Reactions

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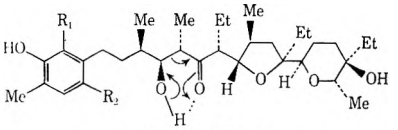
Received April 23, 1973

Investigations into the structure,[1] biosynthesis,[2] nitration,[3] and antibacterial activity[4] of antibiotic X-537A (**1a**) have resulted in the transformation of the



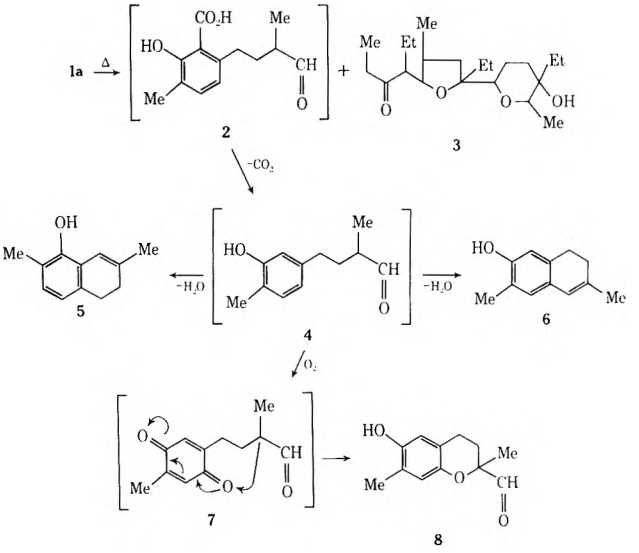
1a, $R_1 = CO_2H$; $R_2 = H$
b, $R_1 = CO_2H$; $R_2 = Br$
c, $R_1 = R_2 = NO_2$

antibiotic into a number of novel compounds. The isolation and characterization of several additional degradation products from **1a** is the subject of this report.

The most useful degradation reaction in the structural and biosynthetic studies on **1a** was the base-catalyzed retroaldol cleavage[1,2] reaction. A competing dehydration reaction[3,4] restricted the yield of the retroaldol ketone **3** to approximately 70%. However, pyrolysis of **1a** has now been shown to give a quantitative yield of **3**, indicating that under pyrolytic conditions, **1a** is degraded *solely via* the retroaldol cleavage route. This reaction is presently under investigation as the basis of a possible pyrolysis–glc method for the assay of **1a**.

The other cleavage product **2** from the pyrolysis of **1a** (Scheme I) spontaneously decarboxylates to the

SCHEME I



phenol **4**, which in turn cyclizes with dehydration to a mixture of 5,6-dihydro-2,7-dimethyl-1-naphthol (**5**) and a 7,8-dihydro-3,6-dimethyl-2-naphthol (**6**). When the antibiotic was heated at 220° for 1 hr in an open tube, 3,4-dihydro-2,7-dimethyl-6-hydroxy-2*H*-1-benzopyran-2-carboxaldehyde (**8**) was isolated in addition to **3**, **5**, and **6**. Production of **8** suggests that, in the presence of air, partial oxidation of the intermediate phenol **4** to a quinone **7** occurred prior to cyclization.

Conversion of **1a** to the 5-bromo derivative **1b** was described in an earlier report.[4] Pyrolysis of **1b** also gave a quantitative yield of the retroaldol ketone **3** together with 3,6-dimethyl-2-naphthol (**9**)[5] and 4-bromo-5,6-dihydro-2,7-dimethyl-1-naphthol (**10**) (Scheme II). The conversion of **1b** into the naphthol **9** in contrast to the 7,8-dihydronaphthol **6** produced on pyrolysis of **1a** was the result of an additional elimination step (loss of HBr) in the case of the bromo derivative. In an analogous reaction, base-catalyzed retroaldol cleavage of **1b** gave 3,6-dimethyl-2-hydroxy-1-naphthoic acid (**11**) whereas base cleavage of **1a** is known[1] to produce the 7,8-dihydro derivative of **11**. Another interesting example of this base cleavage–cyclization reaction was the facile conversion of the dinitrodecarboxy derivative of antibiotic X-537A (**1c**) to 6-hydroxy-2,7-dimethyl-5-nitroquinoline.[3]

(1) J. W. Westley, R. H. Evans, Jr., T. Williams, and A. Stempel, *Chem. Commun.*, 71 (1970).

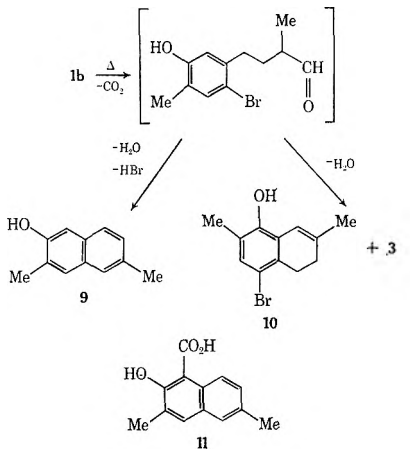
(2) J. W. Westley, R. H. Evans, Jr., D. L. Pruess, and A. Stempel, *Chem. Commun.*, 1467 (1970).

(3) J. W. Westley, J. Schneider, R. H. Evans, Jr., T. Williams, A. D. Batcho, and A. Stempel, *J. Org. Chem.*, **36**, 3621 (1971).

(4) J. W. Westley, E. P. Oliveto, J. Berger, R. H. Evans, Jr., R. Glass, A. Stempel, V. Toome, and T. Williams, *J. Med. Chem.*, **16**, 397 (1973).

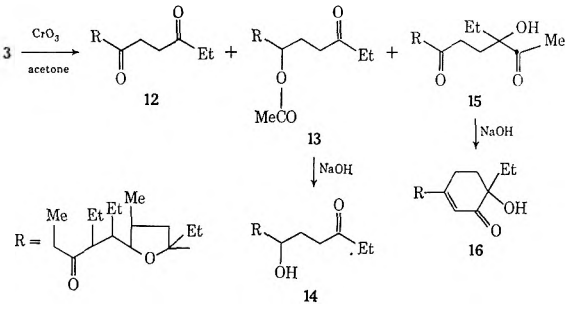
(5) R. Weisgeiner and O. Kruber, *Chem. Ber.*, **52**, 367 (1919).

SCHEME II



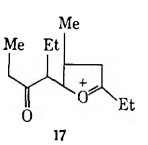
The retroaldol ketone **3** has been further degraded (Scheme III) in connection with our biosynthetic

SCHEME III



studies.[2] In an attempt to isolate the *C*-methyl group in the terminal tetrahydropyranyl ring, **3** was subjected to Jones oxidation.[6] In addition to the desired acetoxy ketone **13**, a triketone **12** was also isolated and characterized. Hydrolysis of **13** in base gave hydroxy ketone **14** and acetic acid. It was from this set of reactions using ^{14}C-labeled substrates that we were able to establish[2] that the terminal C–Me group is biosynthetically derived from acetate in contrast to the other four *C*-methyls in **1a**, which are all propionate derived. When the base hydrolysis reaction was carried out on the crude oxidation product from **3**, the hydroxycyclohexenone **16** was also isolated. The structure of **16** implies the presence of hydroxy triketone **15** in the oxidation mixture from **3**.

Mass spectrometry was essential in determining the structures of compounds **12**, **13**, **14**, and **16**. These compounds, like ketone **3**, all had their base peak at *m/e* 211 which is due to the fragment **17**. This result



indicated that Jones oxidation of **3** caused decomposition only in the tetrahydropyranyl ring.

(6) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N. Y., 1967, p 142.

Experimental Section[7]

Pyrolytic Cleavage of Antibiotic X-537A (1a) under Reduced Pressure to 4-[5-Ethyl-3-methyl-5-(5-ethyl-5-hydroxy-6-methyl-2-tetrahydropyranyl)-2-tetrahydrofuryl]-3-hexanone (3), 5,6-Dihydro-2,7-dimethyl-1-naphthol (5), and 7,8-Dihydro-3,6-dimethyl-2-naphthol (6).—Heating 2.0 g (3.39 mmol) of **1a** under reduced pressure (0.05 mm) at 200° gave 1.69 g of an oily distillate. The oil was chromatographed on 100 g of silica gel using a linear gradient from 1 l. of 1:4 methylene chloride–hexane to 1 l. of methylene chloride. The first fraction was concentrated and crystallized to give 81 mg (14%) of **5**: mp 45–47°; nmr ($CDCl_3$) δ 1.94 (s, 3, CH_3C=), 2.20 (s, 3, aromatic CH_3), 2.20, 2.84 (m, 4, J_{vic} = 8 Hz, CH_2CH_2), 6.47 (s, 1, CH=C), 6.59, 6.82 (AB, 2, J_{ortho} = 9 Hz, aromatic); mass spectrum *m/e* 174 (M^+).

Anal. Calcd for $C_{12}H_{14}O$ (174.23): C, 82.71; H, 8.09. Found: C, 82.53; H, 7.85.

The second fraction gave, on concentration and crystallization, 307 mg (52%) of **6**: mp 140°; nmr ($CDCl_3$) δ 1.85 (s, 3, CH_3C=), 2.16 (s, 3, aromatic CH_3), 2.20, 2.70 (m, 4, J_{vic} = 8 Hz, CH_2CH_2), 6.11 (s, 1, CH=C), 5.71, 6.51 (AX, 2, J_{para} = 1 Hz, aromatic); mass spectrum *m/e* 174 (M^+). *Anal.* Calcd for $C_{12}H_{14}O$ (174.23): C, 82.71; H, 8.09. Found: C, 82.51; H, 8.31.

The third fraction was concentrated to give 1.2 g (100%) of the ketone **3**.[1]

Pyrolysis of Antibiotic X-537A (1a) at Atmospheric Pressure to Give 3,4-Dihydro-2,7-dimethyl-6-hydroxy-2*H*-1-benzopyran-2-carboxaldehyde (8).—Heating 2.0 g (3.39 mmol) of **1a** in an open tube at 220° for 1 hr yielded a heavy black oil. The oil was chromatographed on 250 g of silica gel using a gradient between 2 l. methylene chloride to 2 l. of 1:1 methylene chloride–ether. The first three fractions contained, respectively, **5**, **6**, and **3** and were followed by a fourth fraction which on evaporation gave 400 mg of an oily solid. This material was rechromatographed on 50 g of silica gel using 95:5 benzene–methanol to give a major fraction which was evaporated and crystallized from methylene chloride–hexane to give 171 mg (25%) of **8**: mp 109–111°; nmr ($CDCl_3$) δ 2.13 (s, 3, CH_3CO), 2.23 (s, 3, aromatic CH_3), 2.78, 3.20 (m, 4, J = 7 Hz, CH_2CH_2), 6.81, 7.54 (AX, 2, J_{para} = 1 Hz, aromatic), 9.93 (s, 1, CHO); mass spectrum *m/e* 206 (M^+), 163 (M − 43). *Anal.* Calcd for $C_{12}H_{14}O_3$ (206.23): C, 69.88; H, 6.84. Found: C, 69.61; H, 6.89.

Base Transformation of 5-Bromo Antibiotic X-537A (1b)[4] into 3,6-Dimethyl-2-hydroxy-1-naphthoic Acid (11).—To a solution of 1 g (1.5 mmol) of **1b** in 10 ml of dioxane was added 4 ml of 10% aqueous NaOH. The mixture was stirred for 20 hr at room temperature and then diluted with 20 ml of water and extracted with three 20-ml portions of ethyl acetate. Evaporation of the combined extracts to dryness gave a 75% yield of ketone **3**[1]. The aqueous phase was acidified with 1 *N* HCl and extracted with three 20-ml portions of ether. The combined extracts were evaporated to dryness and the resulting solid was chromatographed on 5 g of silica gel using a linear gradient between methylene chloride and 1:1 methylene chloride–ether. The first fraction eluted from the column was concentrated and crystallized from acetone–hexane to give 37 mg (11%) of **11**: mp 185°; nmr ($CDCl_3$) δ 2.35 (s, 3, aromatic CH_3), 2.41 (s, 3, aromatic CH_3), 7.28 (d of d, 1, J_{meta} = 2, J_{ortho} = 9 Hz, aromatic), 7.40 (d, 1, J_{meta} = 2 Hz, aromatic), 7.61 (s, 1, aromatic), 8.77 (d, 1, J_{ortho} = 9 Hz, aromatic); mass spectrum *m/e* 216 (M^+), 172 (M − CO_2). *Anal.* Calcd for $C_{13}H_{12}O_3$ (216.22): C, 72.20; H, 5.59. Found: C, 71.87; H, 5.41.

Pyrolytic Cleavage of 5-Bromo Antibiotic X-537A (1b)[4] under Reduced Pressure to 3,6-Dimethyl-2-naphthol[5] (9) and 4-Bromo-5,6-dihydro-2,7-dimethyl-1-naphthol (10).—Heating 2.0 g (3 mmol) of **1b** at 174° under reduced pressure (0.05 mm) gave an oily distillate which was dissolved in hexane and chromatographed on 130 g of silica gel using a gradient from 2 l. of hexane to 2 l. of methylene chloride. The first fraction was concentrated to dryness and vacuum distilled at 170° (0.05 mm) to give 75 mg (10%) of **10**: mp 91–92°; nmr ($CDCl_3$) δ 1.93

(7) The ultraviolet spectra were obtained with a Cary Model 14M recording spectrometer. Nuclear magnetic resonance spectra were obtained with a Varian Associates Model A-60 or HA-100 spectrophotometer. Chemical shifts are reported in δ units with the following abbreviations: s, singlet; d, doublet; m, multiplet. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter at 25°. The mass spectra were taken with a CEC-21-110 mass spectrometer at 70 eV.

(s, 3, CH_3C=), 2.14 (s, 3, aromatic CH_3), 2.1, 2.8 (m, 4, J = 7 Hz, CH_2CH_2), 6.39 (s, 1, CH=C), 7.07 (s, 1, aromatic); mass spectrum m/e 252 (M^+). *Anal.* Calcd for $C_{12}H_{13}BrO$ (253.14): C, 56.93; H, 5.18; Br, 31.57. Found: C, 57.19; H, 5.28; Br, 31.68.

The second fraction gave on concentration to dryness and vacuum distillation at 120° (0.05 mm) 36 mg (7%) of **9**: mp 159–162°; nmr ($CDCl_3$) δ 2.37 (s, 3, aromatic CH_3), 2.42 (s, 3, aromatic CH_3), 7.00 (s, 1, aromatic), 7.17 (d of d, J_{meta} = 2, J_{ortho} = 8 Hz, aromatic), 7.45 (d, 1, J_{meta} = 2 Hz, aromatic), 7.51 (d, 1, J_{ortho} = 8 Hz, aromatic); mass spectrum m/e 172 (M^+). *Anal.* Calcd for $C_{12}H_{12}O$ (172.22): C, 83.69; H, 7.02. Found: C, 83.37; H, 6.95.

The third fraction gave on evaporation a 100% yield of ketone **3**.[1]

Oxidation of Ketone 3 to 2-Ethyl-4-methyl-2-(1,4-dioxo-1-hexyl)-5-(4-oxo-3-hexyl)tetrahydrofuran (12) and 2-Ethyl-4-methyl-2-(1-acetoxy-4-oxohexyl)-5-(4-oxo-3-hexyl)tetrahydrofuran (13).—To a solution of 9.16 g (27 mmol) of ketone **3** in 150 ml of acetone was added 25 ml of Jones reagent[6] over 1 hr at room temperature. After a further 16 hr, the reaction solution was diluted with 500 ml of water and extracted with three 500-ml portions of methylene chloride. The pooled extract was washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated under reduced pressure to 8.6 g of an oil. The oil was chromatographed on 400 g of silica gel using a gradient from 1 l. of 1:1 methylene chloride–hexane to 1 l. of methylene chloride followed by a second gradient from 4 l. of methylene chloride to 4 l. of 2:3 methylene chloride–ether. A fraction eluted after 4 l. of solvent had passed through the column gave on evaporation 1.38 g (16%) of **12**: $[\alpha]D$ −12.6° (*c* 1, CH_3OH); ir ($CHCl_3$) 1720 cm^{-1} (CO); uv max (2-propanol) 285 nm (ε 127); mass spectrum m/e 323 (M − 1), 309 (M − CH_3), 295 (M − C_2H_5), 211 (M − 113); nmr ($CDCl_3$) δ 2.50 (m, 8, 4 CH_2CO), 3.60 (m, 1, CHOC). *Anal.* Calcd for $C_{19}H_{32}O_4$ (324.45): C, 70.33; H, 9.94. Found: C, 70.11; H, 9.65.

Immediately following **12**, a second fraction was eluted which on evaporation gave 3.83 g (37%) of **13**: $[\alpha]D$ +20° (*c* 1, CH_3OH); ir ($CHCl_3$) 1715 (ketone), 1730 cm^{-1} (ester); uv max (2-propanol) 281 nm (ε 80); mass spectrum m/e 368 (M^+), 339 (M − C_2H_5), 308 (M − $C_2H_4O_2$), 211 (M − 157); nmr ($CDCl_3$) δ 2.05 (s, 3, CH_3CO), 3.49 (m, 1, CHOC), 4.97 (d of d, 1, $CH_2CHOCOCH_3$, J = 4, 9.5 Hz). *Anal.* Calcd for $C_{21}H_{36}O_5$ (368.50): C, 68.44; H, 9.85. Found: C, 68.73; H, 9.65.

Preparation of 2-Ethyl-4-methyl-2-(1-hydroxy-4-oxo-1-hexyl)-5-(4-oxo-3-hexyl)tetrahydrofuran (14).—To a solution of 1.41 g (3.8 mmol) of acetoxy acetone **13** in 25 ml of methanol was added 19 ml of 10% aqueous NaOH. The reaction mixture was stirred for 18 hr at room temperature and then diluted with 50 ml of water and extracted with three 50-ml portions of ethyl acetate. The extracts were combined, dried (Na_2SO_4), and evaporated to an oil. Distillation of the oil gave 1.2 g (96%) of **14**: bp 170° (0.05 mm); $[\alpha]D$ +18° (c 1, CH_3OH); ir ($CHCl_3$) 1715 (ketone), 3630 cm^{-1} (OH); uv max (2-propanol) 278 nm (ε 102); mass spectrum m/e 326 (M^+), 308 (M − H_2O), 211 (M − 115); nmr ($CDCl_3$) δ 3.55 (m, 1, CHOC), *no* $CHOCOCH_3$. *Anal.* Calcd for $C_{19}H_{34}O_4$ (326.46): C, 69.90; H, 10.50. Found: C, 69.64; H, 10.52.

Preparation of 2-Ethyl-4-methyl-2-(2-ethyl-2-hydroxycyclohex-5-enon-5-yl)-5-(4-oxo-3-hexyl)tetrahydrofuran (16).—To a solution of 484 mg (1.37 mmol) of ketone **3** in 25 ml of acetone was added 1.8 ml of Jones reagent[6] over 1 hr at room temperature. After a further 16 hr, the reaction was diluted with 100 ml of water and extracted with three 100-ml portions of methylene chloride. The extracts were pooled, washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated under reduced pressure to 450 mg of an oil. Without further purification the oil was dissolved in 10 ml of methanol and hydrolyzed using 5 ml of 10% aqueous NaOH. After 18 hr at room temperature the reaction was acidified with 1 *N* HCl and extracted with methylene chloride to give 378 mg of oily product. This product was then chromatographed on 150 g of silica gel using a gradient from 2 l. of methylene chloride to 2 l. of 9:1 methylene chloride–ether. After 2.7 l. of solvent had passed through the column, a uv-absorbing fraction was collected. Evaporation under reduced pressure gave 112 mg (23%) of **16** as a colorless oil: ir ($CHCl_3$) 1670 (C=CCO), 1710 cm^{-1} (CO); uv max (CH_3OH) 238 nm (ε 10,950); nmr ($CDCl_3$) δ 3.58 (m, 1, CHOC), 3.63 (s, 1, OH), 6.14 (s, 1, C=CHCO); mass spectrum m/e 350 (M^+), 335 (M − CH_3), 332 (M − H_2O), 321 (M − C_2H_5), 211 (M − 139). *Anal.* Calcd for $C_{21}H_{34}O_4$ (350.48): C, 71.96; H, 9.78. Found: C, 72.22; H, 9.84.

Acknowledgment.—We are indebted to the Physical Chemistry Department, Hoffmann-La Roche Inc., Nutley, N. J., under the supervision of Dr. R. P. W. Scott, for the analytical and spectral data.

Registry No.—**1a**, 25999-31-9; **1b**, 38784-08-6; **3**, 31478-26-9; **5**, 40919-48-0; **6**, 40919-49-1; **8**, 40919-50-4; **9**, 40919-51-5; **10**, 40919-52-6; **11**, 40919-53-7; **12**, 40919-54-8; **13**, 40919-55-9; **13**, 40919-55-9; **14**, 40919-56-0; **16**, 40919-57-1.

Synthesis of 2,4,6-Triphenyl-1,4-oxazine

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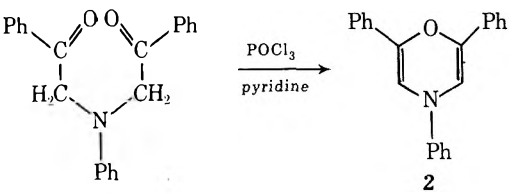
Received January 16, 1973

Although monocyclic 1,4-oxazines are known, only those with an oxygen or nitrogen substituent on the oxazine ring have been prepared.[1] In pursuing studies on the reactions of diphenacylaniline (**1**), the synthesis of a relatively stable, simply substituted oxazine was visualized. Thus, reaction of diphenacylaniline with an excess of $POCl_3$ in pyridine resulted in the formation of a red, crystalline compound with the proposed structure, 2,4,6-triphenyl-1,4-oxazine (**2**).



1 **2**

The oxazine formation can be explained easily by postulating a hemiketal intermediate which undergoes dehydration.

The structure of **2** is based on its analysis, spectral data, and chemical properties. The ir and nmr spectra are particularly informative. In addition to the usual aromatic absorption in the infrared, compound **2** has an intense peak at 1640 cm^{-1}, consistent with the vinyl ether–enamine structure.[2] The nmr spectrum provides additional evidence: a two-proton singlet at δ 6.44 (olefinic hydrogens); a one-proton multiplet centered at δ 6.83 (para hydrogen on aniline moiety); a two-proton multiplet centered at δ 6.95 (ortho hydrogens on aniline moiety); and a 12-proton multiplet centered at δ 7.30 (aromatic hydrogens). The uv spectrum, with absorption at 238 and 348 nm and a weak band at 440 nm, indicates some interaction of the oxazine double bonds with the attached aromatic rings.

The synthesis of **2** proceeded in good yield to give a moderately pure compound, but removal of a remaining impurity, which may be a decomposition prod-

(1) *Cf., e.g.*, G. T. Newbold, F. S. Spring, and W. Sweeny, *J. Chem. Soc.*, 909 (1950); W. Paterson and G. R. Proctor, *Chem. Ind. (London)*, 254 (1961).

(2) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 41.

uct, was difficult. Only by repeated recrystallizations from alcohol under nitrogen was an analytically pure sample obtained. The oxazine was stable in the solid state, but was unstable in certain solutions (*e.g.*, benzene or hexane), particularly in the presence of oxygen. No pure compounds have been isolated from this decomposition.

Compound **2** was unreactive toward $NaBH_4$ and reacted only partially with $LiAlH_4$ in pyridine or boiling alcoholic KOH. As expected, reaction with acid occurred readily. However, acid hydrolysis did not result in the expected regeneration of starting material. Instead, under a variety of conditions, the only substance isolated was a high molecular weight compound of complex structure.

The evidence at hand does not allow a definite structure for this compound or a mechanism for its formation. However, the compound was shown not to arise from diphenacylaniline, since, under the same conditions in which **2** was hydrolyzed (boiling acetic acid), diphenacylaniline reacted only partially and did not produce any of the hydrolysis product. The reactions of **2** will be the subject of future investigations.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Spectral data were obtained from a Perkin-Elmer Model 137 ir spectrophotometer, a Varian A-60 nmr spectrometer, and a Hitachi Perkin-Elmer Model 139 uv–visible spectrophotometer. Analyses were performed by the Chemical Analytical Services, Berkeley, Calif.

Diphenacylaniline (**1**).—A mixture of 3.00 g (15 mmol) of phenacyl bromide, 15 ml of 95% ethanol, 3.15 g of Na_2CO_3, and 0.60 ml (7.5 mmol) of aniline was stirred and heated under reflux for 3 hr. After cooling to room temperature, the solid was filtered and triturated with H_2O for 15 min, then refiltered and recrystallized from pyridine to give 1.40 g (57%) of **1**: mp 237–239° (lit.[3] mp 236–240°); uv λ_{max} (dioxane) 252 nm (ϵ 26,600), 282 (3600); ir 1680 cm^{-1} (Nujol mull).

2,4,6-Triphenyl-1,4-oxazine (**2**).—A mixture of 1.55 g (4.7 mmol) of **1** and 0.87 ml (9.4 mmol) of $POCl_3$ in 30 ml of pyridine (dried over CaH_2) was heated with occasional swirling at 100° for 45 min. The deep red solution was poured onto 50 ml of crushed ice and the resulting solid was filtered. Two recrystallizations from isopropyl alcohol gave 0.81 g (55%) of red needles, mp 167–180°. This material was 80–90% pure and contained an impurity with a carbonyl peak at 1680 cm^{-1}. Use of a nitrogen atmosphere for the reaction did not materially affect the yield or purity of the product. However, repeated recrystallization from alcohol under nitrogen gave a small amount (72 mg) of an analytically pure sample: mp 183–185°; uv (EtOH) λ_{max} 238 nm (ϵ 19,800), 348 (20,400), 440 (3100); ir (CS_2) strong absorption at 1640, 1250, 1040, 750, and 685 cm^{-1}; nmr (CS_2) δ 6.44 (s, 2 H), 6.83 (m, 1 H), 6.95 (m, 2 H), 7.30 (m, 12 H). *Anal.* Calcd for $C_{22}H_{17}NO$: C, 84.85; H, 5.51; N, 4.50. Found: C, 84.68; H, 5.40; N, 4.71.

Acid Hydrolysis of 2.—A mixture of 298 mg (0.96 mmol) of **2**, 35 ml of 95% ethanol, and 4 ml of concentrated HCl was heated to reflux for 30 min. The light yellow solid, which formed on cooling, was filtered and crystallized from 40% isopropyl alcohol–cyclohexane to give 71 mg (0.125 mmol) of colorless crystals with a waxy appearance, mp 231–234°. Recrystallization gave crystals: mp 236–238° uv (EtOH) λ_{max} 240 nm (sh, ϵ 17,200), 330 (36,500); ir (CS_2) strong absorption at 1655, 1240, 755, and 690 cm^{-1}; nmr (CS_2) δ 6.50 (m, 2 H), 6.75 (m, 4 H), 7.14 (m, 24 H). *Anal.* Calcd for $C_{40}H_{30}N_2O_2$: C, 84.19; H, 5.30; N, 4.91; mol wt, 572. Found: C, 84.39; H, 5.44; N, 4.76; mol wt 545 (Rast).

Registry No.—**1**, 41120-12-1; **2**, 41120-13-2; phenacyl bromide, 532-27-4; aniline, 62-53-3.

(3) G. K. Almstrom, *Justus Liebigs Ann. Chem.*, **411**, 350 (1916).

A Double Perkow Reaction. 1,3-Butadiene-2,3-diol Bis(dialkyl phosphate)

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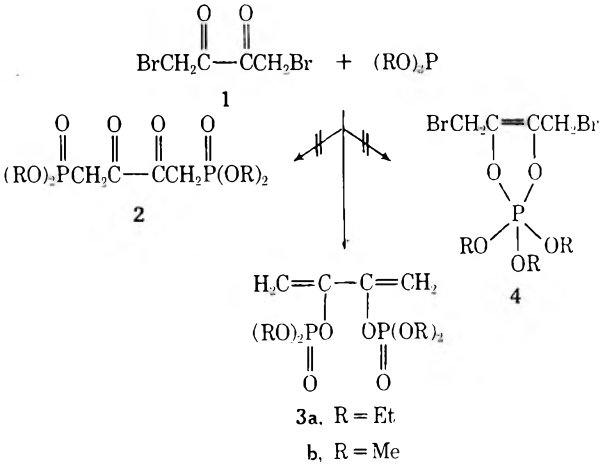
Received May 22, 1973

Trialkyl phosphites are known to react with α-halo ketones to yield β-ketophosphonates and/or vinyl phosphates (Arbuzov[1] and Perkow[2] products, respectively) and with nonhalogenated ketones and α diketones to yield phosphoranes.[3] In view of these results, an examination of the reactions of trialkyl phosphites with 1,4-dibromo-2,3-butanedione (**1**) was of interest. This ketone is capable of yielding all of these types of product, *i.e.*, phosphonates (**2**), phosphates (**3**), and phosphoranes (**4**), and allows an assessment of the competition between the three processes.



The addition of 2 mol of triethyl phosphite to a 1 *M* ethereal solution of **1** gave **3a** (98%) in an exothermic reaction. The ir spectrum of **3a** exhibited a characteristic olefinic stretching band (1602 cm^{-1}), but was transparent in the carbonyl region. The ^1H nmr spectrum consisted of a methyl triplet at τ 8.70, a methylene octet at 5.88, and a vinyl multiplet at 4.82. A broadened quintet at +6.8 ppm was observed in the ^{31}P nmr spectrum. These data are only consistent with structure **3a** and are inconsistent with either structure **2** or **4**. Similar results were obtained in the reaction of **1** with trimethyl phosphite; the ir and nmr data obtained for **3b** were similar to those cited for **3a**.

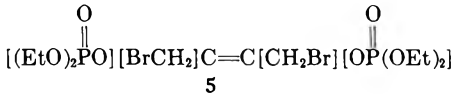
Further evidence for the proposed structure was provided by the absorption of 2 equiv of hydrogen by **3b** (atmospheric pressure, Pd/C). Reduction of the ethyl analog **3a** was inexplicably more difficult but was accomplished at 60 psi in methanol using 5% Ru/C–

(1) (a) G. M. Kosolapoff, "Organo-Phosphorus Compounds," Wiley, New York, N. Y., 1950; (b) P. C. Crofts, *Quart. Rev., Chem. Soc.*, **12**, 341 (1958); (c) M. Grayson and E. J. Griffith, "Topics in Phosphorus Chemistry," Wiley, New York, N. Y., 1964; (d) R. F. Hudson, "Structure and Mechanism in Organo-Phosphorus Chemistry," Academic Press, London, 1965.

(2) (a) F. W. Lichtenthaler, *Chem. Rev.*, **61**, 607 (1961); (b) P. A. Chopard, V. M. Clark, R. F. Hudson, and A. J. Kirby, *Tetrahedron*, **21**, 1961 (1965).

(3) (a) F. Ramirez, *Pure Appl. Chem.*, **9**, 337 (1964); (b) F. Ramirez, *Accounts Chem. Res.*, **1**, 168 (1968).

$PdCl_2$ as catalyst. Bromination of **3a** afforded the 1,4-addition product **5** as a white solid.



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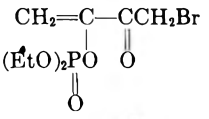
Reaction of an equimolar mixture of triethyl phosphite and **1** was also exothermic and afforded, exclusively, the mono Perkow product **6** (96%). Hence,

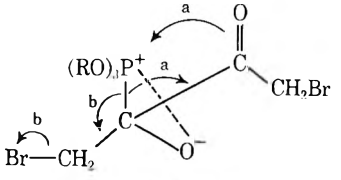


6

the double Perkow product **3a** must arise sequentially with the rate of formation for the first vinyl phosphate group being considerably faster than that for the second.

Vinyl phosphates **3a**, **3b**, and **6** were thermally labile to the extent that purification was not possible by either gas chromatographic or distillation techniques. **3a** and **3b** were nevertheless storage stable for several months at −10°, while **6** decomposed within 1 week at that temperature.

Recent studies suggest that the formation of both vinyl phosphates[4] and phosphoranes[5] proceeds by a mechanism involving initial attack of phosphorus on carbonyl carbon. By applying such a scheme to **1** the corresponding β-ketophosphonium intermediate **7** is generated which may undergo cyclization (route a) as



7

occurs with 2,3-butanedione[6] or bromine elimination (route b) as occurs with bromoacetone.[7] That in fact vinyl phosphates (route b) exclusively arise can be rationalized in terms of the entropy factor. A pathway involving loss of alkyl bromide is favorable because it would result in an entropy increase, whereas cyclization to phosphorane would further constrain the system.

Arbuzov products (2) might be expected to arise by direct SN2 displacement of bromine by phosphorus. Because the carbonyl carbon in **1** is the most electrophilic site, a result of the electron-withdrawing groups $BrCH_2$– and –$COCH_2Br$, direct nucleophilic displacement of bromine cannot compete successfully. Thus, while other pathways are seemingly available, the preference of **1** to form double Perkow products is noteworthy.

(4) (a) I. J. Borowitz, M. Anschel, and S. Firstenberg, *J. Org. Chem.*, **32**, 1723 (1967); (b) I. J. Borowitz, S. Firstenberg, G. B. Borowitz, and D. Schuessler, *J. Amer. Chem. Soc.*, **94**, 1623 (1972).

(5) Y. Ogata and M. Yamashita, *J. Amer. Chem. Soc.*, **92**, 4670 (1970).

(6) F. Ramirez and N. B. Desai, *J. Amer. Chem. Soc.*, **92**, 2652 (1960).

(7) A. N. Pudovik, *Dokl. Akad. Nauk SSSR*, **105**, 735 (1955); *Chem. Abstr.*, **50**, 11230g (1956).

Experimental Section

Melting points are corrected. Ir spectra were scanned on the neat smears (KBr or NaCl plates) using Perkin-Elmer 257 and 521 spectrophotometers. Nmr spectra were obtained with Varian Associates A-60A (^1H) and XL-100-15 (^{31}P) spectrometers operating at ambient temperature. Chemical shifts are in parts per million relative to internal TMS (τ 10) and external 85% orthophosphoric acid for the ^1H and ^{31}P resonances, respectively. The ^{31}P spectra were stabilized with ^2H internal lock. Elemental analysis were performed by Galbraith Laboratories, Knoxville, Tenn. High resolution mass spectra were obtained on an AEI MS 902S spectrometer with a DS 30 Data System.

1,3-Butadiene-2,3-diol Bis(diethyl phosphate) (3a).—To a magnetically stirred solution of 1,4-dibromo-2,3-butanedione (12.2 g, 0.050 mol) in 50 ml of absolute diethyl ether was added dropwise triethyl phosphite (16.6 g, 0.10 mol). An ice–water bath was used to maintain the reaction temperature below 10°. After the mixture stirred for 2 hr at 10°, the solvent was removed *in vacuo* and 17.7 g (0.049 mol. 98%) of an orange liquid (**3a**) was obtained: ir bands at 1602 (m, C=C), 1276 (s, P=O), 878 (m) cm^{-1}; ^1H nmr (CCl_4) τ 8.70 (12 H, t, J^3_{PH} = 7.5 Hz, CH_3CH_2O), 5.88 (8 H, octet, J^3_{PH} = 8.5 Hz, CH_2CH_2OP), 4.82 (4 H, m, vinyl); ^{31}P nmr (CCl_4) +6.8 ppm (br quintet, J_{PH} = 8.0 Hz); mass spectrum (70 eV) *m/e* calcd for $C_{12}H_{24}O_8P_2$, 358.0970 (found, 358.0993).

1,3-Butadiene-2,3-diol Bis(dimethyl phosphate) (3b).—In a procedure similar to that described above, reaction of 1,4-dibromo-2,3-butanedione (12.2 g, 0.050 mol) and trimethyl phosphite (12.4 g, 0.10 mol) gave 12.9 g (0.042 mol, 85%) of an orange liquid (**3b**): ir bands at 1602 (m, C=C), 1276 (s, P=O), 883 (m), 852 (m), 822 (m) cm^{-1}; ^1H nmr (CCl_4) τ 6.21 (12 H, d, J^3_{PH} = 11 Hz, CH_3OP), 4.80 (6 H, m, vinyl); ^{31}P nmr (CCl_4) +4.4 ppm (br septet, J_{PH} = 11 Hz); mass spectrum (70 eV) *m/e* calcd for $C_8H_{16}O_8P_2$, 302.0319 (found, 302.0313).

Hydrogenation of 3a.—A solution of 6.9 g (19 mmol) of **3a** in 150 ml of absolute methanol was placed in a Parr hydrogenation apparatus along with a catalyst system comprising 5% ruthenium on charcoal (1.5 g) and palladium chloride (0.1 g). Reduction proceeded over a 6-day period under 50–60-psi hydrogen gas pressure. Work-up consisted of filtration through Celite and solvent evaporation from the filtrate. A sweet-odored liquid (6.1 g) was obtained. The ir spectrum of this product was transparent in the olefinic region.

Hydrogenation of 3b.—A magnetically stirred solution of **3b** (1.5 g, 5.0 mmol) in 25 ml of ethyl acetate was reduced with gaseous hydrogen over 5% rhodium on charcoal in a typical microhydrogenation apparatus. The extent of hydrogen absorption (10 mmol) corresponded to the reduction of two double bonds. The solution was subsequently filtered through Celite and the solvent was removed *in vacuo* from the filtrate. The product (1.25 g) exhibited an ir spectrum devoid of olefinic bands in the 1600-cm^{-1} region.

1,4-Dibromo-2-butene-2,3-diol Bis(diethyl phosphate) (5).—Bromine (4.8 g, 0.030 mol) was added dropwise to a solution of **3a** (10.7 g, 0.030 mol) in 50 ml of carbon tetrachloride. The reaction appeared to be facile as noted by the rate of disappearance of the 1602-cm^{-1} band. After the mixture stirred for 0.5 hr, the solvent was removed *in vacuo* to give an orange liquid that crystallized at room temperature within several hours. The product was recrystallized from a small amount of ether at −78° followed by rapid collection and drying on a sintered-glass funnel. A white powder (6.1 g, 0.012 mol, 39% yield) was obtained and identified as **5**: mp 64–65°; ir bands at 1670 (w, C=C), 1272 (s), 1218 (s), 1025 (s) cm^{-1}; ^1H nmr (CCl_4) τ 8.61 (12 H, t, J^3_{HH} = 7.5 Hz, CH_3CH_2O), 5.80 (8 H, octet, J^3_{PH} = 7 Hz, CH_3CH_2OP), 5.66 (4 H, s, CH_2Br); ^{31}P nmr (CCl_4) +37.3 ppm (quintet, J_{PH} = 7 Hz).

Anal. Calcd for $C_{12}H_{24}Br_2O_8P_2$: C, 26.80; H, 4.65; Br, 30.80; P, 12.00. Found: C, 27.03; H, 4.62; Br, 31.06; P, 11.92.

Decomposition of **5** was noticeable when it was left standing overnight at room temperature.

Diethyl 1-Bromoacetylvinyl Phosphate (6).—Triethyl phosphite (8.3 g, 0.050 mol) was added dropwise to a solution of 1,4-dibromo-2,3-butanedione (12.2 g, 0.050 mol) in 50 ml of absolute diethyl ether. The reaction exotherm was moderated with an ice–water bath keeping the temperature below 10°. After the solution had stirred for 1.5 hr at 10°, the solvent was removed *in vacuo*. An orange liquid (14.5 g, 0.048 mol, 96% yield) remained which was identified as 6: ir bands at 1701 and 1691 (m, C=O), 1612 (m, C=C), 1274 (s, P=O), 830 (m) cm^{-1}; ^1H nmr (CCl_4) τ 8.67 (6 H, t, J^3_{HH} = 7 Hz, CH_3CH_2O), 5.80 (4 H, octet, J^3_{PH} = 8.5 Hz, CH_3CH_2OP), 5.58 (2 H, s, CH_2Br), 4.27, 3.99 (2 H, pair of t, J^2_{HH} = 3 Hz, J^4_{PH} = 3 Hz, vinyl); mass spectrum (70 eV) *m/e* calcd for $C_8H_{14}BrO_5P$, 299.9760 (found, 299.9769).

Acknowledgment.—We are indebted to Professor C. E. Griffin for critical review of the manuscript and for helpful discussions. We thank Professor R. W. Parry for use of his spectrometer (XL-100-15).

Registry No.—**3a**, 41189-14-4; **3b**, 41189-15-5; **5**, 41189-16-6; **6**, 41189-17-7; 1,4-dibromo-2,3-butanedione, 6305-43-7; triethyl phosphite, 122-52-1; trimethyl phosphite, 121-45-9.

Novel Synthesis of γ-Keto Esters

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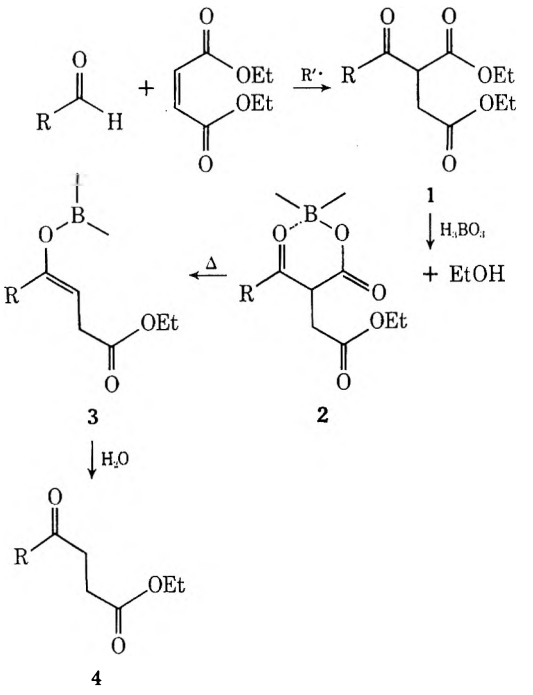
One method for the preparation of γ-keto esters proceeds *via* acid[1] or alkaline[2] saponification of an acylated succinic diester followed by decarboxylation and reesterification to the desired γ-keto ester. The attractive feature of this process is the ready availability of a variety of acylated succinic diesters.[3] The disadvantages of the process are the relatively low overall yield and the fact that the intermediate γ-keto acid has to be reesterified to the desired γ-keto ester.

We now wish to report a high yield, direct conversion of acylated diethyl succinates to the corresponding γ-keto esters.

The starting materials, acylated diethyl succinates, are readily available *via* radical-induced addition of aldehydes to diethyl maleate.[3] These keto diesters, when heated in the presence of boric acid, yield, after aqueous work-up, the desired γ-keto ester in one step (Scheme I).

Indications are that the reaction proceeds to a complexed borate ester intermediate **2** *via* a selective transesterification process. It is reasonable to assume that the ability of the ketocarbonyl group to complex to the boron atom is responsible for the high selectivity in the transesterification step. This type of reaction sequence is experimentally supported by the collection of ethanol[4] prior to the onset of decarboxylation. The intermediate borate ester **2** thus formed would appear to be ideally suited to undergo decarboxylation and this indeed takes place readily at temperatures around 160–170°. The product, after decarboxylation, is an enol

SCHEME I



borate of type **3**, from which the free γ-keto ester **4** is liberated by an aqueous work-up procedure.

The yields obtained for the transformations **1** → **4** are summarized in Table I.

TABLE I

1	Registry no.	4 (% isolated yield[a])	Registry no.
R = ethyl	41117-76-4	77	3249-33-0
R = *n*-propyl	41117-77-5	80	14369-94-9
R = *n*-hexyl	41117-78-6	80	14294-63-4

[a] Satisfactory physical data have been obtained for all isolated γ-keto esters **4**.

Experimental Section[5]

Since the procedure is general, only the preparation of 4-oxohexanoic acid ethyl ester (**4**, R = ethyl) is described.

Diethyl propionylsuccinate[3] (92.0 g, 0.4 mol) and boric acid (24.6 g,[6] 0.4 mol) were heated to 150° (oil bath, magnetic stirring, Claisen condenser connected with a gas measuring device). Within 1 hr, 11.7 g of distillate (mainly ethanol) and ~0.75 l. of gas were collected. As the temperature was raised to 170°, the rate of CO_2 evolution increased and a total of 8.3 l. of gas was collected after 1.5 hr. At this time, CO_2 evolution was almost at a standstill and the reaction mixture had a clear, light yellow appearance (total reaction time, 2.5 hr; vpc analysis of a sample showed the reaction mixture to contain only very little starting material). The contents of the flask were cooled to room temperature, poured onto ice–water (550 ml), and extracted with toluene (3 × 180 ml). After the combined organic layers were dried over anhydrous $MgSO_4$, the solvent was removed *in vacuo* and the residue was distilled through a 10-cm Vigreux apparatus. A main fraction of 48.6 g (77%), bp 109–112° (18 mm[7]), was collected. Vpc analysis indicated the material to be of 99.2% purity (area comparison).

Acknowledgment.—We thank the staff of our Physical Chemistry Department (Direction, Dr. R. P. W. Scott) for the determination of spectral data.

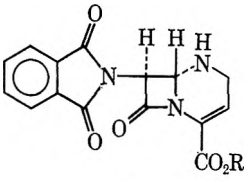
(1) A. Franke and A. Kroupa, *Monatsh.*, **69**, 167 (1936).
(2) E. Friedman, *J. Prakt. Chem.*, **146**, 159 (1936).
(3) T. M. Patrick, Jr., *J. Org. Chem.*, **17**, 1009, (1952).
(4) As characterized by comparative vpc and mass spectrometry.
(5) Vpc conditions: Hewlett-Packard Model 5720 with dual flame detector; column 6 ft × 0.125 in o.d. stainless steel; 10% UCW-98 on Diatoport 5, programmed at 30°/min from 50 to 250°.
(6) No attempts were made to use <1 mol of boric acid/mol of **1**.
(7) Bp 95–98° (11 mm): M. I. Ushakov and V. F. Kucherov, *J. Gen. Chem. USSR*, **14**, 1073 (1944); *Chem. Abstr.*, 7185 (1946).

See Editorial, *J. Org. Chem.* **37**, No. 19, 4A (1972).

Studies on Lactams. XXIX.[1] Synthesis of Aza Analogs of Cepham

Summary: The synthesis of several novel aza analogs of cephams has been accomplished by the reaction of N-acylated 1,4,5,6-tetrahydropyrimidines with different acid chlorides in presence of triethylamine.

Sir: Recently Wolfe, *et al.*,[2] have reported the conversion of penicillin to 1-aza-6-epidethiocephem (**1**).

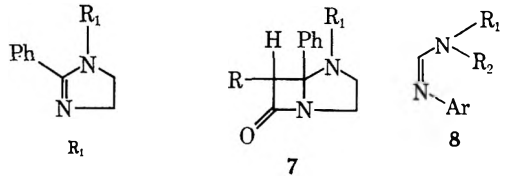


1

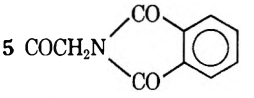
Prompted by the disclosure of this partial synthesis we describe here the results of our studies on the total synthesis of analogous compounds. In view of our earlier success with the "acid chloride–imine" method[3] for preparing various α-substituted β-lactams including 6-epipenicillin methyl ester,[4] we investigated the use of this synthetic approach to penam and cepham analogs in which S has been replaced by N.

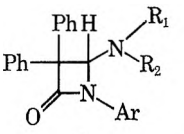
Our initial attempt involved the reaction of 2-phenylimidazoline (**2**) with azidoacetyl chloride in presence of triethylamine. The reaction product appeared to contain the expected bicyclic β-lactam (**7**, R = N_3; R_2 = $COCH_2N_3$) on the basis of ir and nmr spectral data. However, **7** could not be obtained in the pure form: attempts at purification led to its decomposition and only an *N*-acylimidazoline **3** could be isolated. This was not surprising in view of our earlier experience[5] with unstable β-amino-β-lactams **9** obtained from amidines **8** and diphenylketene. Reaction of **3** with an acid chloride and triethylamine was no more successful in leading to pure **7**. Several other *N*-acyl derivatives, such as **4**, **5**, and **6**, fared no better than **3** for obtaining pure 1-azapenam analogs.

Next we condensed **10**, the higher homolog of **2**, with phenoxyacetyl chloride and triethylamine in methylene chloride solution. The desired β-lactam **13** was obtained in 72% yield: mp 131–132°; ir ν_{max} 1775 (β-lactam CO), 1667 cm^{-1} (amide CO); nmr ($CDCl_3$) τ 2.3–3.4 (m, 15 H), 4.25 (s, 1 H), 5.25 (s, 2 H), 5.68–6.5 (br, 2 H), 6.5–7.2 (br, 2 H), 7.9–8.78 (br, 2 H); mass spectrum M^+ at *m/e* 428. Calcd for $C_{26}H_{24}N_2O_4$: C, 72.89; H, 6.54; N, 5.60. Found: C, 72.75; H, 6.77; N, 5.96. Under similar conditions azido acetyl chloride (**10**) and triethylamine gave the diazido-β-lactam (**14**). Catalytic hydrogenation of **14** on Pd/C produced a diamino-β-lactam (**15**) which upon acylation with phenoxyacetyl chloride (2 mol) provided the cepham analog **16** with two phenoxyacetamido side chains. It is possible to have two different side chains: conversion of **10** to **11** and **12** prior to reaction with phenoxyacetyl chloride and triethylamine led to the β-lactams **17** and **18**, respectively. Because of the presence of several substituents in close proximity in compounds **13**–**18**, assignment of configuration of these β-lactams on the base of nmr data does not appear to be possible.



7 **8**

Compd	R_1
2	H
3	$COCH_2N_3$
4	$COCH_2OPh$
5	
6	p-$SO_2C_6H_4CH_3$



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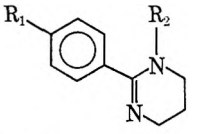
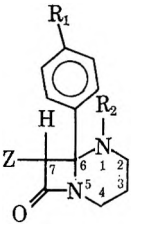


Compd	R_1	R_2
10	H	H
11	H	p-$SO_2C_6H_4CH_3$
12	CO_2Et	$COCH_2Ph$



Compd	Z	R_1	R_2
13	OPh	H	$COCH_2OPh$
14	N_3	H	$COCH_2N_3$
15	NH_2	H	$COCH_2NH_2$
16	$NHCOCH_2OPh$	H	$COCH_2NHCOCH_2OPh$
17	OPh	H	p-$SO_2C_6H_4CH_3$
18	OPh	CO_2Et	$COCH_2Ph$

It is reasonable to expect that the various routes described previously for placing[6] and modifying[7] α substituents in monocyclic β-lactams prepared by the

(1) For part XXVIII, see A. K. Bose, J. C. Kapur, B. Dayal, and M. S. Manhas, *Tetrahedron Lett.*, in press.

(2) S. Wolfe, J. Ducep, G. Kannengiesser, and W. S. Lee, *Can. J. Chem.* **50**, 2902 (1972).

(3) A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya, and M. S. Manhas, *Tetrahedron*, **23**, 4769 (1967).

(4) A. K. Bose, G. Spiegelman, and M. S. Manhas, *J. Amer. Chem. Soc.*, **90**, 4506 (1968).

(5) A. K. Bose and I. Kugajevsky, *Tetrahedron*, **23**, 957 (1967).

(6) M. S. Manhas and A. K. Bose, "beta-Lactams: Natural and Synthetic," part 1, Wiley-interscience, New York, N. Y., 1971.

(7) A. K. Bose, H. P. S. Chawla, B. Dayal, and M. S. Manhas, *Tetrahedron Lett.*, 2503 (1973).

"acid chloride–imine" method would also be applicable to the synthesis of bicyclic β-lactams from suitable tetrahydropyrimidine derivatives. The striking increase in stability in going from the 1-azadethiopenam to the corresponding cepham series, of course, facilitates the synthesis of cepham analogs. The extension of this general synthetic approach to other bicyclic β-lactams is in progress.

Acknowledgment.—We are indebted to Gist-Brocades N. V., The Netherlands, and Stevens Institute of Technology, for support of this research.

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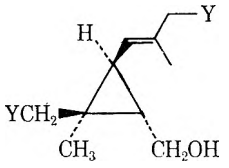
RECEIVED JUNE 4, 1973

Asymmetric Induction in a [2,3] Sigmatropic Rearrangement. A Biogenetic Model

Summary: Treatment of achiral *S*-methyl-*S*,*S*-bis-(γ,γ-dimethylallyl)sulfonium fluoroborate with chiral bases produces artemisia methyl thioether with 5–12% asymmetric induction.

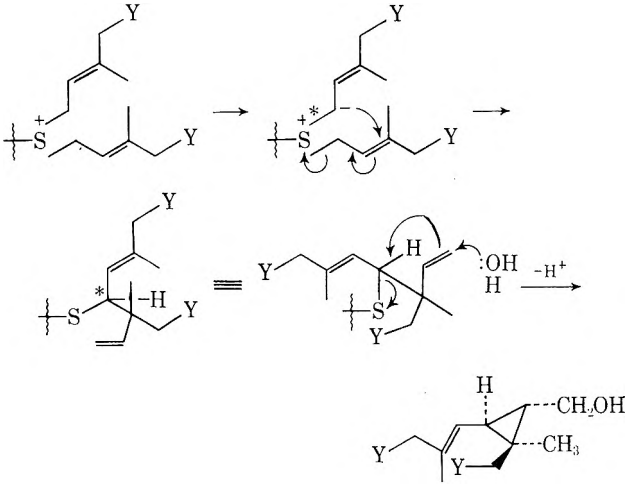
Sir: The discovery that the direct biological precursors of squalene[1,2] and phytoenes[3] possess the cyclopropane structures **1b** and **1c**, respectively, suggests a link to the monoterpene analog chrysanthemol (**1a**).



1a, Y = H
b, Y = geranyl
c, Y = farnesyl

Among the biogenetic schemes considered for the formation of these compounds,[4] that based on the [2,3] sigmatropic rearrangement of sulfur ylides possesses exceptional fascination (see Scheme I).[4g,5] In this scheme, the chirality of the biogenetic intermediates **1a–c** is determined by a single event—the conversion of an achiral sulfonium salt into a chiral ylide.

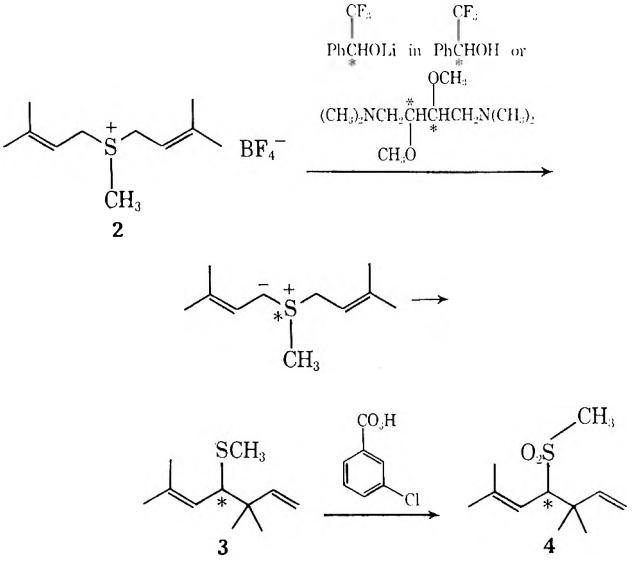
SCHEME I
[2,3] SIGMATROPIC REARRANGEMENT BIOGENETIC HYPOTHESIS



In experiments designed to examine various facets of this scheme, consideration of the stereochemistry of the process was undertaken to determine whether (1) simple chiral bases could discriminate between the enantiotopic[6] arms of the achiral sulfonium salt, (2) the ylide thus generated could rearrange faster than it loses its asymmetry, and (3) the chirality at sulfur could be faithfully translated into chirality at carbon.

Treatment of *S*-methyl-*S*,*S*-bis(γ,γ-dimethylallyl)-sulfonium fluoroborate (**2**) with *n*-butyllithium–sparteine complex[7] or lithium 1-(−)-menthoxide in tetrahydrofuran led to artemisia methyl thioether **3** with no observable optical rotation (see Scheme II). On the

SCHEME II
REARRANGEMENT IN MODEL SYSTEM[a]



[a] * indicates chiral atom.

(1) (a) L. J. Altman, R. C. Kowerski, and H. C. Rilling, *J. Amer. Chem. Soc.*, **93**, 1782 (1971); (b) H. C. Rilling, C. D. Poulter, W. W. Epstein and B. Larsen, *ibid.*, **93**, 1783 (1971); (c) W. W. Epstein and H. C. Rilling, *J. Biol. Chem.*, **245**, 4597 (1979); (d) H. C. Rilling and W. W. Epstein, *J. Amer. Chem. Soc.*, **91**, 1041 (1969).

(2) (a) J. Edmond, G. Popjak, S.-M. Wong, and V. P. Williams, *J. Biol. Chem.*, **246**, 6254 (1971); (b) R. V. M. Campbell, L. Crombie, and G. Pattenden, *Chem Commun.*, 218 (1971); (c) R. M. Coates and W. H. Robinson, *J. Amer. Chem. Soc.*, **93**, 1785 (1971).

(3) L. J. Altman, L. Ash, R. C. Kowerski, W. W. Epstein, B. R. Larsen, H. C. Rilling, F. Muscio, and D. E. Gregonis, *J. Amer. Chem. Soc.*, **94**, 3257 (1972).

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(5) (a) J. E. Baldwin, R. E. Hackler, and D. P. Kelley, *J. Amer. Chem. Soc.*, **90**, 4758 (1968); (b) G. E. Risinger and H. D. Durst, *Tetrahedron Lett.*, 3133 (1968); (c) B. M. Trost and R. LaRochelle, *ibid.*, 3327 (1968); (d) G. M. Blackburn, W. D. Ollis, C. Smith, and I. O. Sutherland, *Chem. Commun.*, 99 (1969).

(6) In actuality, this terminology is incorrect. Since the carbanion may be tetrahedral the ylide may exist in one of four diastereomeric forms in which case the two arms are diastereotopic. Making the reasonable assumption that the carbanion center is at least "effectively" planar owing to rapid inversion simplifies the discussion. No conclusions are affected by this assumption.

(7) H. Nozaki, T. Aratani, and T. Toraya, *Tetrahedron Lett.*, 4097 (1968).

other hand, treatment of salt **1** with lithium (*R*)-(−)-2,2,2-trifluorophenylethoxide in 1:1 (*R*)-(−)-2,2,2-trifluorophenylethanol[8]–pentane at −10° led to thioether **3** in 54% yield with $[\alpha]^{25}D$ −1.45 ± 0.12° (*c* 4.12, $CHCl_3$). Use of (*S*)-(+)-alcoholate in its corresponding alcohol under the same conditions generated thioether **2** with $[\alpha[^{25}D$ +1.12 ± 0.54° (*c* 5.56, $CHCl_3$). To evaluate the optical purity of the thioethers, use of the chiral shift reagent tris[(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium[9] [henceforth abbreviated $Eu(CFP)_3$] was made. While separation of the signals for the *S*-CH_3 groups in the enantiomers could be achieved, cleaner results were obtained by oxidizing the thioether to the sulfone **4** (mp 38.5–40°) in 99% yield with *m*-chloroperbenzoic acid in ether at 0°. By addition of 21.7 mol % of $Eu(CFP)_3$ to a $CDCl_3$ solution of the racemic thioether, the CH_3SO_2 signal shifts from δ 2.74 to two singlets of equal intensity at 3.74 and 3.82. Treatment of the thioether of $[\alpha]^{25}D$ −1.45° in this way generated the corresponding sulfone, $[\alpha]^{25}_{365}$ −3.48 ± 0.18° (*c* 1.09, $CHCl_3$), in which the nmr spectrum showed a 5 ± 1% difference in the peak heights (average of 11 values) with the methyl singlet at highest field being the larger.

The use of optically active 1,4-bis(dimethylamino)-2,3-dimethoxybutane as solvent has been shown to enhance the optical yields in organometallic additions.[10] Rearrangement of the salt **2** with lithium (*S*)-(+)-2,2,2-trifluorophenylethoxide in a 1:1 mixture of dry tetrahydrofuran and (*S,S*)-(+)-1,4-bis(dimethylamino)-2,3-dimethoxybutane under nitrogen at −20° generated thioether **3** in 48% yield with $[\alpha]^{25}_{365}$ +2.90 ± 0.30° (*c* 0.62, $CHCl_3$). Oxidation with *m*-chloroperbenzoic acid as above gave the sulfone of $[\alpha]^{20}_{365}$ +6.33 ± 0.70° (*c* 1.43, $CHCl_3$) whose nmr spectrum in the presence of $Eu(CFP)_3$ indicated an enantiomeric purity of 12 ± 2% (average of 22 values) in which the downfield CH_3SO_2 singlet was the more intense. The net optical yield observed represents the optical yields for proton abstraction and ylide rearrangement.

In a related case, the [2,3] sigmatropic rearrangement has been found to proceed with >94% optical induction.[11] This observation suggests that in the present case the optical induction observed represents the preference in the proton abstraction step. The unusually high optical yields for such a process in this simple base system would clearly support a contention that in the highly asymmetric environment of an enzyme system such a process would exhibit complete optical induction. The demonstration that a great deal of the stereochemical control is inherent in the chemistry of such systems suggests more serious attention should be given to the hypothesis of Scheme I as a possible biogenetic model.

(8) W. H. Pirkle, S. D. Beare, and T. G. Burlingame, *J. Org. Chem.*, **34**, 470 (1968); H. M. Peters, D. M. Feigl, and H. S. Mosher, *ibid.*, **33**, 4245 (1968).

(9) (a) H. L. Goering and J. N. Eikenberry, unpublished results. For a related reagent, see H. L. Goering, J. N. Eikenberry, and G. S. Koermer, *J. Amer. Chem. Soc.*, **91**, 5913 (1971). (b) R. R. Fraser, M. A. Petit, and M. Miskow, *ibid.*, **94**, 3253 (1972). (c) R. R. Frazer, M. Petit, and J. K. Saunders, *Chem. Commun.*, 1450 (1971).

(10) D. Seebach, H. Dorr, B. Bostani, and V. Ehrig, *Angew. Chem., Int. Ed. Engl.*, **8**, 982 (1969).

(11) B. M. Trost and R. F. Hammen, *J. Amer. Chem. Soc.*, **95**, 962 (1973). For related work, see J. E. Baldwin and J. E. Patrick, *ibid.*, **93**, 3556 (1971); V. Rautenstrauch, *Chem. Commun.*, 4 (1970); R. K. Hill and T. H. Chan, *J. Amer. Chem. Soc.*, **88**, 866 (1966).

Acknowledgment.—We wish to thank the National Institutes of Health and the National Science Foundation for their generous support of our programs. We wish to thank Professor Dieter Seebach for a generous sample of (*S,S*)-(+)-1,4-bis(dimethylamino)-2,3-dimethoxybutane and Professor Harlan Goering for a generous sample of $Eu(CFP)_3$.

(12) Camille and Henry Dreyfus Teacher–Scholar Grant Recipient.

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RECEIVED MAY 17, 1973

Rearrangement of Pyruvates to Malonates. β-Lactams by Ring Contraction

Summary: Periodate treatment of α-keto-γ-lactams results in rearrangement with ring contraction to β-lactams.

Sir: Numerous methods for the synthesis of β-lactams by ring closure or ring expansion have been developed,[1] but there are very few methods using ring contraction.[2] We have found that the oxidative rearrangement of α-ketoacyl derivatives with periodate, which has been reported for both acyclic and cyclic α-keto esters and amides,[3] appears to be generally extensible to the synthesis of β-lactams by oxidative ring contraction of α-keto-γ-lactams.

For example, the monocyclic α-ketolactam, 1-methyl-2,3-pyrrolidinedione (**2**), rearranges to 3-carboxy-1-methyl-2-azetidinone (**3**). The bicyclic compounds, **5a–c**, rearrange to bicyclic β-lactams, **6a–c**. When the β substituent, R_1 in **5**, is hydrogen or methyl, only one of the two possible isomers is obtained; however, when R_1 is bromine, both isomers are formed. The synthesis and rearrangement of these α-ketolactams, **2** and **5a–c**,[4] are presented below.

4-Ethoxycarbonyl-1-methyl-2,3-pyrrolidinedione (**1**),[5] heated in refluxing 2.9 *M* HCl (50 min), followed by extraction[6] and sublimation, gave 1-methyl-2,3-pyrrolidinedione (**2**, 63%, mp 89–91°). Reaction of **2** with periodate (pH 7.0, 24 hr), followed by destruction of excess periodate with bisulfite, extraction at pH 4.0, and chromatography on silica gel, gave 3-carboxy-1-methyl-2-azetidinone (**3**, 30%), ir 1745 (br) cm^{-1}.

1-Azabicyclo[4.3.0]nonane-8,9-dione (**5a**, 60%, mp 62–66°) was obtained from 7-ethoxycarbonyl-1-azabicyclo[3.2.0]nonane-8,9-dione (**4a**),[7] by an analogous

(1) Summarized in M. S. Manhas and A. K. Bose, "beta-Lactams: Natural and Synthetic," part 1, Wiley-Interscience, New York, N. Y., 1971.

(2) (a) S. N. Ege, *Chem. Commun.*, 759 (1968); (b) M. F. Chasle and A. Foucaud, *C. R. Acad. Sci., Ser. C*, **268**, 2034 (1969); (c) G. Lowe and D. D. Ridley, *Chem. Commun.*, 328 (1973).

(3) M. L. Rueppel and H. Rapoport, *J. Amer. Chem. Soc.*, **94**, 3877 (1972).

(4) All new compounds have been characterized spectrally (ir in $CHCl_3$ and nmr in $CDCl_3$). Elemental compositions were established by combustion analyses and mass spectra.

(5) P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1087 (1956).

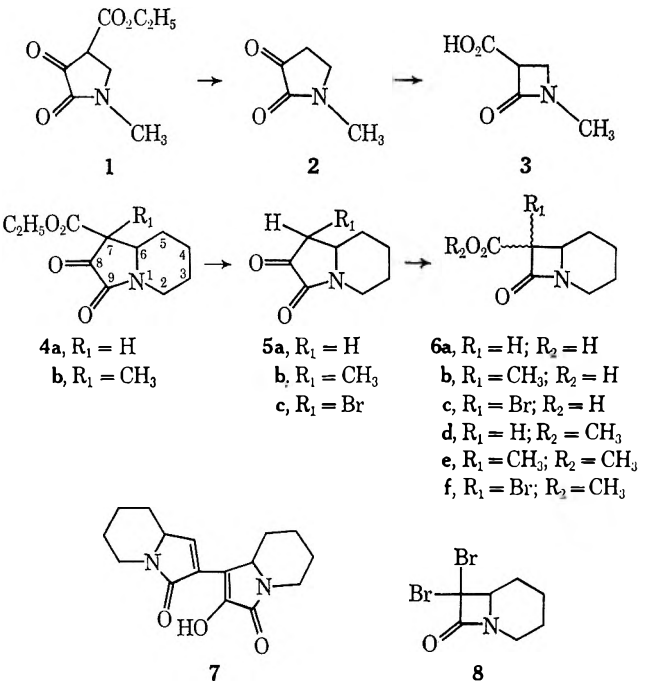
(6) Owing to high water solubility, most of the reported compounds were isolated from aqueous solution by continuous extraction with methylene chloride.

(7) R. Adams, S. Miyano, and M. D. Nair, *J. Amer. Chem. Soc.*, **83**, 3323 (1961).

procedure (reflux time 2.5 hr). Chromatographing **5a** on silica with $CHCl_3$ resulted in self-condensation to **7** [mp 219–224° dec; nmr δ 0.8–2.5 (m, 12 H), 2.6–3.2 (m, 2 H), 3.7–4.5 (m, 4 H), 6.59 (d, J = 2.2 Hz, 1 H), 12.9 (s, 1 H); uv (C_2H_5OH) 249 nm (ε 12,300), 297 (14,200)], a facile self-condensation also observed with other α-keto-γ-lactams.[5] Reaction of **5a** with excess periodate in lithium phosphate buffer (pH 6.3) was complete in 20 min, determined by the decrease in absorbance at 223 nm, and crystallization (acetone–hexane) of the extracted product gave 7-carboxy-8-oxo-1-azabicyclo[4.2.0]octane (**6a**): 70%; mp 145–146°; nmr δ 1.1–2.3 (m, 6 H), 2.5–3.1 (m, 1 H), 3.5–4.1 (m, 2 H), 3.75 (d, J = 1.8 Hz, 1 H), 9.2 (s, 1 H); ir 1753, 1722 cm^{-1}.[8] The 1.8-Hz coupling constant establishes the C-6 and C-7 protons as trans;[9] no evidence for any cis isomer was found. Esterification of **6a** with diazomethane gave **6d** and gas chromatography[10] of this ester gave a single symmetrical peak.

7-Ethoxycarbonyl-7-methyl-1-azabicyclo[4.3.0]nonane-8,9-dione (**4b**, mp 92–93°), obtained[11] in 30% yield by refluxing for 18 hr a benzene solution of diethyl 3-methyl-2-oxosuccinate[12] with an ether–ethanol solution of 2 molar equiv of 1-piperidiene,[13] was hydrolyzed and decarboxylated as described for the synthesis of **2** (reflux time 1.5 hr), resulting in 7-methyl-1-azabicyclo[4.3.0]nonane-8,9-dione (**5b**, 74%, mp 191–193°). Reaction of **5b** with periodate gave 7-carboxyl-7-methyl-8-oxo-1-azabicyclo[4.2.0]octane (**6b**): 50%; mp 179–181°; ir 1743, 1713 cm^{-1}; nmr δ 1.2–2.1 (m, 6 H), 1.52 (s, 3 H), 2.5–3.0 (m, 1 H), 3.6–4.0 (m, 2 H), 10.6 (s, 1 H). Gas chromatography of **6e** methyl ester (ir 1756, 1725 cm^{-1}), obtained from **6b** with diazomethane, gave a singly symmetrical peak.[10]

The bromo analog, 7-bromo-1-azabicyclo[4.3.0]-nonane-8,9-dione (**5c**, mp 121–122° from chloroform–hexane), obtained in 80% yield from **5a** by reaction with cupric bromide in methylene chloride and treated with periodate as previously described, gave a 40% yield of 7-bromo-7-carboxy-8-oxo-1-azabicyclo[4.2.0]-octane (**6c**) as a mixture of stereoisomers. Gas chromatography[10] of **6f** methyl esters (obtained from **6c** with diazomethane) indicated the presence of two isomers in the ratio of 1:9. Also present were products subsequently shown to arise from decomposition of the minor isomer of **6f** during gas chromatography; no decomposition of the major isomer took place. Column chromatography on kieselgel with 3:1 ether–petroleum ether (bp 30–60°) permitted establishing the structures of the two major decomposition products as 7,7-dibromo-8-oxo-1-azabicyclo[4.2.0]octane (**8**) [mp 73–74°; nmr δ 1.2–2.3 (m, 6 H), 2.5–3.1 (m, 1 H), 3.5–4.0 (m, 2 H); ir 1782 cm^{-1}] and **6d**. The two isomers



1 2 3

4a, R_1 = H
b, R_1 = CH_3

5a, R_1 = H
b, R_1 = CH_3
c, R_1 = Br

6a, R_1 = H; R_2 = H
b, R_1 = CH_3; R_2 = H
c, R_1 = Br; R_2 = H
d, R_1 = H; R_2 = CH_3
e, R_1 = CH_3; R_2 = CH_3
f, R_1 = Br; R_2 = CH_3

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of **6f**, separated by column chromatography on kieselgel with 3:1 ether–petroleum ether, were hydrolyzed to the respective acids **6c** with 1 equiv of potassium hydroxide in 50% aqueous dioxane (room temperature, overnight). The major isomer had double mp 97 and 119–120°; nmr δ 1.2–2.2 (m, 6 H), 2.6–3.1 (m, 1 H), 3.6–4.1 (m, 2 H); ir 1772, 1724 cm^{-1}. The minor isomer had mp 180–182°; nmr δ 1.1–2.3 (m, 6 H), 2.6–3.1 (m, 1 H), 3.6–4.1 (m, 2 H); ir 1777, 1719 cm^{-1}.

Formation of β-lactams by this oxidative ring contraction reaction thus proceeds under mild conditions and appears to be generally applicable. The method provides a route for introduction of difunctionality at the α position of the β-lactam and is compatible with the presence of a number of substituents. Its scope is being further investigated.

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RECEIVED JULY 2, 1973

(8) Both the cis and trans isomers of the ethyl and *tert*-butyl esters of **6a** have been synthesized by a different method: G. Lowe and J. Parker, *Chem. Commun.*, 577 (1971).

(9) H. B. Kagan, J. J. Basselier, and J. L. Luche, *Tetrahedron Lett.*, 941 (1964); K. D. Barrow and T. M. Spotswood, *ibid.*, 3325 (1965).

(10) Chromatography was carried out on a 5 ft × 0.25 in. column of 5% QF-1 on Chromosorb W (80–100), AW-DMCS, at 175° and a He flow rate of 132 ml/min: T_R of **6e** = 3.9 min; T_R of **6d** = 4.3 min; T_R of **6f** (major) = 7.1 min; T_R of **6f** (minor) = 8.1 min.

(11) Based on the method used for the synthesis of 6-ethoxycarbonyl-1-azabicyclo[3.3.0]octane-7,8-dione: B. M. Goldschmidt, *J. Org. Chem.*, **27**, 4057 (1962).

(12) C. Clerc-Bory and C. Mentzer, *Bull. Soc. Chim. Fr.*, 436 (1958).

(13) Prepared by following the procedure used for the synthesis of 1-pyrroline: D. W. Fuhlhage and C. A. Van der Werf, *J. Amer. Chem. Soc.*, **80**, 6249 (1958).

A Versatile Prostaglandin Synthesis. Use of a Carboxy-Inversion Reaction

Summary: Ring contraction of the dione **5** gave the cyclopentenone **6** which was readily elaborated to the mixed peranhydride **17**; the latter then is transformed *via* a carboxy inversion reaction to **18**, a known precursor leading to the racemic prostaglandins E_2 and $F_{2\alpha}$.

Sir: By elimination of the hydroxyl group at the C-11 position in PGE_1 or PGE_2 to give either the PGA or 11-deoxy derivatives, the effects associated with the PGE compounds, *e.g.*, smooth muscle and antilipolytic properties, have been lost whereas the effect on blood

pressure has been retained or even intensified.[1] This observed separation of activities makes the C-11 position an interesting one for further modification.

Of the various total syntheses of the natural prostaglandins there are none which may be easily adapted to the preparation of ring analogs at the C-11 position while at the same time allowing for modifications of both side chains.[2] This communication describes such a scheme.

Treatment of 5-carboxy-1,3-cyclohexanedione (**1**)[3] with allyl alcohol and a catalytic amount of *p*-toluenesulfonic acid produced 3-allyloxy-5-(2-propenyloxycarbonyl)-2-cyclohexen-1-one (**2**). Refluxing crude **2** in acetic anhydride[4] for 8 hr afforded the rearranged enol acetate **3** which when treated with 1 equiv of lithium methoxide in methanol gave the dione **4**[5,6] (70% overall yield from **1**), mp 133–134°. Chlorination with 1 equiv of *tert*-butyl hypochlorite in methanol at 0° produced the chloro derivative **5**[5–7] (95%), bp 130° (0.01 mm), which was smoothly converted by treatment with 10 equiv of sodium carbonate in refluxing mesitylene for 1.5 hr to the ring-contracted[8] cyclopentenone **6**[5,6] (78% yield), uv max 226 nm (ϵ 7790), bp 84–86° (0.01 mm).

Reaction of the ketone **6** with excess nitromethane and a catalytic amount of "Triton B" for 3.5 hr at 65° yielded the 1,4 adduct **7**[5,6] (88% yield), purified on a 5:1 silica gel column using 5% ethyl acetate–benzene as eluent (homogeneous by tlc and gas chromatographic analysis). Oxidation of the allyl side chain with 1.1 equiv of sodium permanganate in a sulfuric acid–water–acetone solution gave the acid derivative **8**[5,6,9] (83% yield), mp 149–150°. Treatment of **8** with 1.1 equiv of lithium methoxide and 4 equiv of sodium borohydride in methanol afforded a mixture of alcohols which, after refluxing for 1 hr in THF followed by extraction of the residue with sodium bicarbonate, gave the lactone **10**[5,6] (carbonyl absorption ($CHCl_3$) at 5.6 and 5.72 μ, mp 102–103° (54% based on starting ketone **8**). Acidification of the bicarbonate solution afforded the alcohol **9**,[5,6] mp 98–100°. The alcohol **9** may be recycled by oxidation with 1.1 equiv of permanganate to give the starting ketone **8**. Alternatively the reduction of **8** with 2 equiv of lithium perhydro-9b-boraphenalylhydride[10] in THF at −78° showed a high degree of selectivity and produced a single alcohol (compound **9** was not detected by tlc) which was converted as previously described to the lactone **10** (88% yield). A confirmation of the stereochemical orientation shown for **10** was obtained from an X-ray analysis of a *p*-bromoanilide derivative, mp 189°, obtained from the acid **11**,[5,6] mp 125–126° (from hydrolysis of **10** in a dilute sulfuric acid–tetrahydrofuran solution at reflux for 24 hr).

We next turned our attention to the elaboration of the allylic alcohol side chain. Treatment of **10** with 1.1 equiv of lithium methoxide in methanol at 0° gave the lithium nitronate which after drying (high vacuum for several hours) was dissolved in a saturated aqueous solution of sodium tetraborate[11] and oxidized with 0.95 equiv of sodium permanganate[12,13] at 0° to give the aldehyde **12**[5,6] (70%), mp 93–94°. The aldehyde **12** was smoothly converted to the *trans*-enone lactone **13**[5,6] (70% yield), uv max 224 nm (ϵ 15,900), mp 48–49°, by treatment with the sodio derivative of dimethyl-2-oxoheptylphosphate in dimethoxyethane at 25° for 1.5 hr.[14] Reduction of the enone **13** with excess zinc borohydride in dimethoxyethane at 20° for 1 hr afforded a 95% yield of the 15α-hydroxy-11α-methoxycarbonyl lactone[15] (**14**) and the 15β isomer (ratio of ~1:1). The desired 15α isomer **14**,[5,6] mp 58–61°, was separated from the mixture by chromatography on silica gel using ether as the eluent. Saponification of **14** in a methanol–water (9:1) solution containing 2.2 equiv of sodium hydroxide at 50° for 1 hr gave after acidification and refluxing for 1 hr in THF the oily acid **15**[5,6] (92% yield). Acetylation of **15** with pyridine and acetic anhydride produced the 15α-acetoxy derivative **16**[5,6] (93% yield), mp 34–36°. Treatment of **16** with 1 equiv each of dicyclohexylcarbodiimide[16] and *m*-chloroperbenzoic acid (>98%) in ether–methylene chloride (1:1) at 0° for 15 hr produced the mixed peranhydride **17**[5,6] (61% yield), mp 79–80°, which, when refluxed in acetonitrile for 1.5 hr, undergoes a carboxy-inversion[17] reaction with *retention of configuration*[18] to give, after treatment with lithium methoxide (1 equiv) of the resultant mixed carbonate, the diol **18**[5,6] (35% yield). Compound **18** was identical in all respects with an authentic sample.[19] This intermediate has previously been converted to the racemic prostaglandins $F_{2\alpha}$ and E_2.

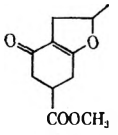
Compound **14** has been used to prepare 11-deoxy-11-carboxyprostaglandins as well as other 11-deoxy C-11 analogs[20] derived *via* modification of the carboxy group.

(1) J. E. Pike, F. P. Kupiecke, and J. R. Weeks in "Nobel Symposium 2 Prostaglandins," S. Bergstrom and B. Samuelson, Ed., Interscience, New York, N. Y., 1966.

(2) For leading references to active side chain analogs, see A. P. Labhsetwar, *Nature*, **238**, 400 (1972); E. W. Yankee and G. L. Bundy, *J. Amer. Chem. Soc.*, **94**, 3651 (1972); B. J. Magerlein, The 165th National Meeting of the American Chemical Society, Dallas, Texas, April 1973, Topics in Medicinal Chemistry Symposium.

(3) E. E. van Tamelen, *J. Amer. Chem. Soc.*, **78**, 4405 (1956).

(4) When the rearrangement is carried out in solvents other than acetic anhydride, a substantial quantity of the dihydrofuran (i) is formed.



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(5) Ir and nmr (at 60 MHz) spectra were in agreement with the assigned structure.

(6) Satisfactory elemental or mass spectral analytical data were obtained.

(7) The nmr spectra indicates the product to be a mixture of two isomers (ratio of 3:1).

(8) G. Büchi and B. Egger, *J. Org. Chem.*, **36**, 2021 (1971). A similar ring contraction has recently been employed for the preparation of (±)-11-deoxyprostaglandin [J. Bagli and T. Bogri, *Tetrahedron Lett.*, 3817 (1972)].

(9) Preliminary experiments using (+) -and (−)-α-phenylethylamine afforded the (+) acid, mp 112–113°, $[\alpha]^{25}D$ +84.28° (c 1.01, CH_3OH), and the (−) acid, mp 111–112°, $[\alpha]^{25}D$ −79.9° (c 1.15, CH_3OH).

(10) H. C. Brown and W. C. Dickason, *J. Amer. Chem. Soc.*, **92**, 709 (1970).

(11) If the sodium tetraborate was not employed (pH 9–10), the aldehyde **12** was always contaminated with nitro derivative **10**.

(12) H. Shechter and F. T. Williams, Jr., *J. Org. Chem.*, **27**, 3699 (1962).

(13) The lithium nitronate under various conditions of the Nef reaction always resulted in incomplete conversion and the contamination of the aldehyde **12** with substantial quantities of the starting nitro derivative **10**.

(14) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5675 (1969).

(15) Prostaglandin numbering.

(16) F. D. Greene and J. Kazan, *J. Org. Chem.*, **28**, 2168 (1963).

(17) D. B. Denney and N. Sherman, *J. Org. Chem.*, **30**, 3760 (1965).

(18) T. Kashiwagi, S. Kozuka, and S. Oae, *Tetrahedron*, **26**, 3619 (1970).

(19) Kindly supplied by Professor E. J. Corey.

(20) Several 11-substituted 11-deoxyprostaglandins have recently been obtained *via* the 1,4 addition to the methyl ester of PGA_2 obtained from marine sources [C. V. Grudzinskas and M. J. Weiss, *Tetrahedron Lett.*, 141 (1973)].

In addition, starting from compound 1 (X = alkyl, H), various C-11 alkylprostaglandins and C-11 deoxyprostaglandins have been synthesized. By varying the

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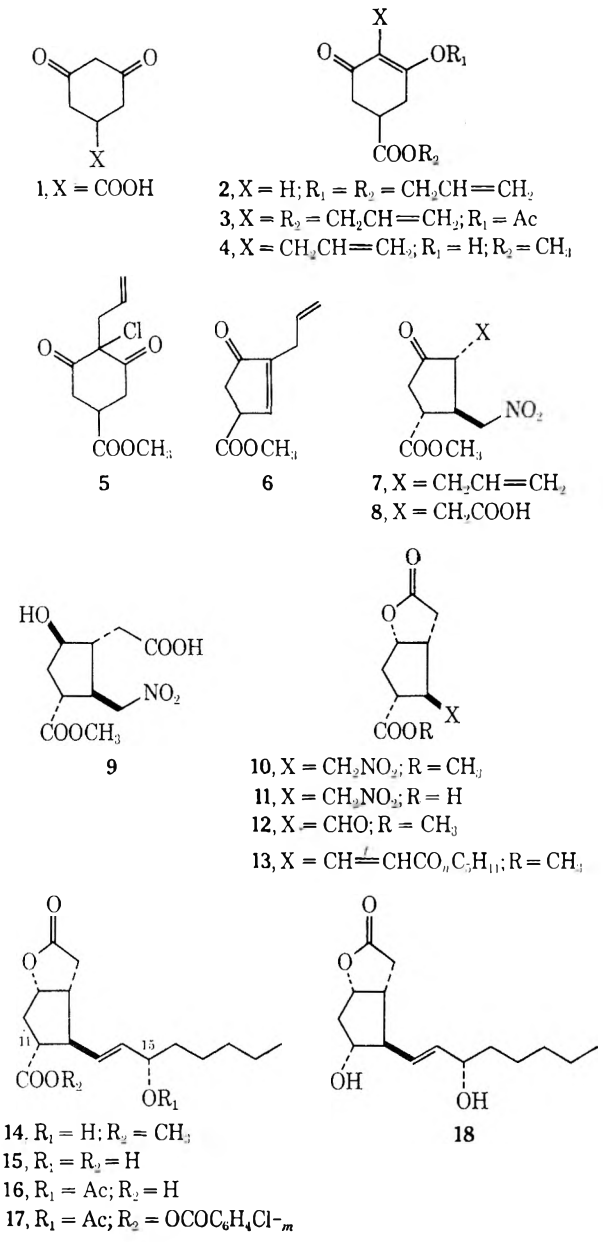

type of Wittig reagent used, various side-chain analogs have also been prepared. Description of this work is in preparation.

Acknowledgment.—The authors wish to thank Professor G. Büchi and Dr. E. P. Oliveto for their interest and stimulating discussions of this work. We also wish to thank Dr. J. F. Blount for X-ray analysis, Dr. W. Benz, Dr. V. Toome, Dr. T. Williams, and Mr. S. Traiman for mass, uv, nmr, and ir spectra, respectively, as well as Dr. F. Scheidl for the microanalyses.

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RECEIVED MAY 29, 1973

The Oxymercuration of *cis*- and *trans*-Di-*tert*-butylethylene. Evidence for a π-Bridged Intermediate

Summary: The methoxymercuration of *cis*-di-*tert*-butylethylene proceeds by an anti addition without molecular rearrangement or carbon–carbon bond rotation providing evidence for a π-bridged intermediate.

Sir: The intermediacy of mercurinium ions in the oxymercuration reaction has been the subject of recent controversy. Arguments for[1] and against[2] the involvement of these mercury-bridged π complexes have recently appeared in the literature. Although kinetic studies[3] have not yet provided evidence for mercurinium ions under oxymercurating conditions, they have been observed in solution[4] and in the gas phase.[5] We now report convincing evidence for significant π bridging in the oxymercuration of the highly strained *cis*-di-*tert*-butylethylene (**1**). Our results also clearly demonstrate that alkene strain energy is not a dominant factor in the rate of oxymercuration of alkenes.

On the basis of theoretical calculations[6] and photoelectron spectroscopy,[7] **1** has been determined to be essentially a planar alkene with relief of steric repulsions of the *tert*-butyl groups being manifested by in-plane angle distortion (C–C–*tert*-butyl bond angle, 136°). The ground-state energy of **1** is 10.2 kcal/mol[8] higher in energy than the relatively unstrained *trans*-di-*tert*-butylethylene (**2**). The difference in strain energy between **1** and **2** provides a unique opportunity to examine the question as to whether the steric repulsion between the *cis*-*tert*-butyl groups is sufficient to destabilize the π-bridged mercurinium ion by C_1–C_2 bond rotation affording a free carbonium ion.

Methoxymercuration of **1** with $Hg(ClO_4)_2$ in methanol solvent followed by Cl^- treatment afforded *dl*-*threo*-3-(chloromercuri)-4-methoxy-2,2,5,5-tetramethylhexane (**3**)[9] by the preferred anti addition[10] (eq 1). The structural assignment of **3** was based on the vicinal H_1–H_2 coupling constant[11] ($J_{H_1,_2}$ = 1.6 Hz) and on the nmr chemical-shift difference[12] of the methoxyl resonance in carbon tetrachloride and pyridine solvent. Methoxymercuration of **2** with $Hg(ClO_4)_2$ also afforded the threo isomer **3** by a syn addition to the double bond. This provides the first example of a syn addition to an unstrained alkene in the oxymercuration reaction and

(1) D. J. Pasto and J. A. Gontarz, *J. Amer. Chem. Soc.*, **93**, 6902 (1971); R. D. Bach and R. F. Richter, *ibid.*, **94**, 4747 (1972), and references cited therein.

(2) H. C. Brown and K.-T. Liu, *J. Amer. Chem. Soc.*, **93**, 7335 (1971).

(3) J. Halpern and H. B. Tinker, *J. Amer. Chem Soc.*, **89**, 6427 (1967).

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(7) M. B. Robin, G. N. Taylor, N. H. Kuebler, and R. D. Bach, *J. Org. Chem.*, **38**, 1049 (1973).

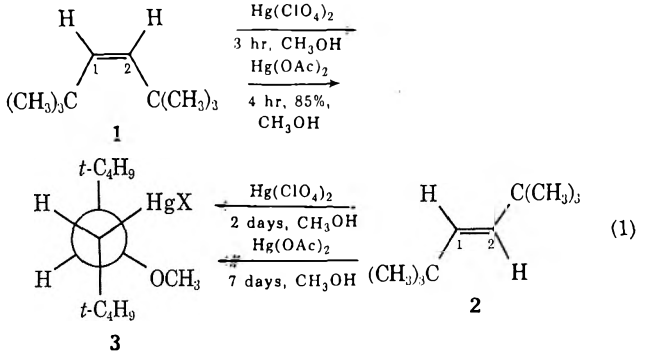
(8) J. D. Rockenfeller and F. D. Rossini, *J. Phys. Chem.*, **65**, 267 (1961).

(9) The compound had mp 85.5–87°; ir (CCl_4) 1040 cm^{-1} (COC); nmr (CCl_4) 213.7 Hz (s, 3), δ 3.15 (d, 1, J = 1.6 Hz), 2.13 (d, 1, J = 1.6 Hz), 0.99 (s, 9).

(10) W. Kitching, *Organometal. Chem. Rev.*, **3**, 61 (1968).

(11) The *dl*-dichloride derived from anti addition of Cl_2 to **1** has a ^{13}C–H coupling constant of 0.8 Hz while the meso isomer has a coupling constant of 5.2 Hz: R. C. Fahey, *J. Amer. Chem. Soc.*, **88**, 4681 (1966).

(12) R. F. Richter, J. C. Philips, and R. D. Bach, *Tetrahedron Lett.*, 4327 (1972).



clearly demonstrates that enhanced reactivity is not a prerequisite for syn addition.

Since it is generally accepted that an increase in alkene ground-state energy due to bond angle strain will accelerate the rate of oxymercuration, in the absence of twist strain[13] effects, we were quite surprised to observe that the relative rate of methoxymercuration of **1** with mercuric acetate was 10^3 times *as slow as* the unstrained cyclohexene. Moreover, **2** did not exhibit a measurable reactivity toward $Hg(OAc)_2$ over a 7-day period.[14] This result is precisely the opposite to that which would be predicted on the basis of the relative rates of the chlorination of **1** and **2** where the relative rate ratio k_{trans}/k_{cis} had a value of 2.7.[11] Since both olefins are essentially planar,[7] steric effects must play the dominant role in the lack of reactivity and in the syn addition to **2**.

Since the angle strain in **1** results from cisoid repulsion of the bulky *tert*-butyl groups, we thought that it would be of interest to measure the relative rate of methoxymercuration of cyclobutene where angle compression strain but no steric effects are involved. Again angle strain resulted in a decrease in relative rate and the methoxymercuration of cyclobutene was only 0.36 relative to cyclohexene despite the fact that the preferred anti addition was involved in both cases. Moreover, the relative rate of oxymercuration of norbornene, which affords a syn adduct, was only 4.5 times as fast as cyclohexene and, in fact, bicyclo[2.2.2]octene exhibited a relative rate of only 0.03.[15] *trans*-Cyclooctene, which has torsional strain (the double bond is twisted ~20° out of plane[7] resulting in 9.2 kcal/mol of strain energy relative to the cis isomer), methoxymercurates at a rate of only 10.1 times as fast as cyclohexene. Indeed, 1-octene exhibits a rate of methoxymercuration comparable to that of *trans*-cyclooctene and is 9.5 times as fast as that of cyclohexene. However, the comparatively faster rate (10^4) of methoxymercuration of *trans*-cyclooctene *via* a syn mode of addition relative to the anti mode of addition to **1**, which has a comparable strain energy, is indeed striking and, therefore, demands a reevaluation of the effects of strain energy on the rate of oxymercuration reactions with alkenes.

Several factors argue against a carbonium ion mechanism in the oxymercuration reaction. For example, only 1,2 addition to 1,3-dienes has been observed in the absence of structural rearrangement or conjugate addition. Theoretical calculations[5,17] also suggest that mercurinium ions prefer to be planar in the absence of steric strain and are stabilized principally by $\sigma-\pi$ conjugation without development of significant charge at carbon. The lack of carbonium ion rearrangements during the syn oxymercuration of **2** is consistent with this hypothesis. Moreover, bromination of **2** in methanol solvent, where an appreciable charge at carbon develops,[17] afforded only rearranged products with no methoxy bromination being detected. Therefore, stereospecific anti addition to **1**, in addition to the absence of olefin isomerization or molecular rearrangements due to carbonium ion formation, strongly suggests that the extent of π bridging in the transition state is comparable to or greater than the 10.2-kcal/mol strain energy in **1**.

Further corroboration for the mercurinum ion stability comes from deoxymercuration studies. It may be inferred from Kreevoy's kinetic data[18] on deoxymercuration that the enthalpy of activation for a syn deoxymercuration is ~5 kcal/mol higher than the anti deoxymercuration. In support of this, oxymercuration and deoxymercuration of *cis*- and *trans*-stilbene[19] has been shown to be completely stereospecific (the ground-state energy difference between the isomeric olefins is 4.5 kcal/mol). Deoxymercuration of **3**, with concentrated HCl, afforded exclusively the trans isomer **2** which is compelling evidence for an unprecendented syn deoxymercuration in an acyclic system. Thus, a semiquantitative limit to steric inhibition for the preferred trans deoxymercuration reaction may now be placed between 4.5 and 10.2 kcal/mol.

Thus, it may be concluded that the oxymercuration of **1** proceeds *via* a bridged mercurinium ion intermediate. The relative rates observed provide dramatic evidence that significant relief of strain in the transition state for oxymercuration is not attained. These results are, therefore, consistent with the formation of an olefin π complex with subsequent attack by solvent in the rate-limiting step.

Acknowledgment is made to the National Institutes of Health (ES00761-02) for support of this work. We also wish to thank Dr. Gary N. Taylor for a generous supply of *cis*- and *trans*-di-*tert*-butylethylene and for helpful discussions concerning the mechanism of addition.

(13) T. G. Traylor, *Accounts Chem. Res.*, **2**, 152 (1969).

(14) This result precludes the possibility that **1** is isomerized to **2** prior to oxymercuration with $Hg(OAc)_2$. Control experiments and the nmr spectrum of the reaction mixture have also established that isomerization of **1** is not occurring under the reaction conditions.

(15) Similar observations have been made in the hydroxymercuration of these alkenes: H. C. Brown and P. J. Geohegan, *J. Org. Chem.*, **37**, 1937 (1972). Control experiments have established that alkene exchange reactions are slow under our experimental conditions. We have shown that olefin exchange reactions of oxymercurials are quite facile and relative rate studies must distinguish between the kinetic and thermodynamic products.[16]

(16) R. D. Bach, R. N. Brummel, and R. F. Richter, *Tetrahedron Lett.*, 2879 (1971).

(17) R. D. Bach and H. F. Henneike, *J. Amer. Chem. Soc.*, **92**, 5589 (1970); R. D. Bach and P. A. Scherr, *ibid.*, **94**, 220 (1972).

(18) M. M. Kreevoy, J. W. Gilje, L. T. Ditsch, W. Batorewicz, and M. A. Turner, *J. Org. Chem.*, **27**, 726 (1962).

(19) G. F. Wright, *Ann. N. Y. Acad. Sci.*, **65**, 436 (1957); M. M. Kreevoy, private communication.

(20) Lubrizol Fellow, 1972–1973.

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JUNE 6, 1973

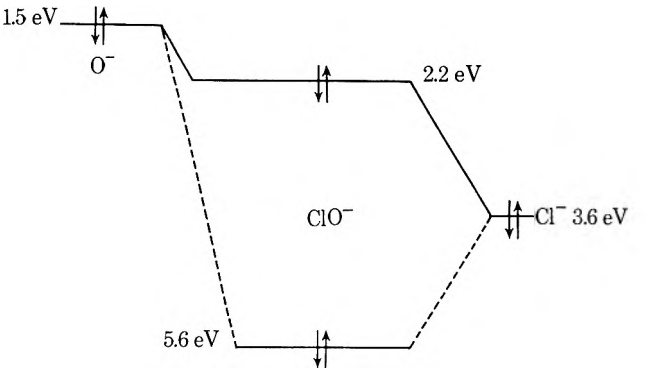
Aromatic Transition States and the α Effect

Summary: An explanation for the α effect (enhanced reactivity of nucleophiles possessing an unshared electron pair adjacent to the nucleophilic center) is offered; an aromatic transition state is proposed and analyzed in terms of Zimmerman's Möbius–Hückel approach.

Sir: It is often observed that certain nucleophiles show an enhanced reactivity relative to analogous species with similar pK values. These rapidly reacting nucleophiles are characterized by a lone pair of electrons adjacent to the nucleophilic site. This structural feature has caused the increased reactivity to be termed the "α effect." [1] Since only a few systematic studies have been carried out,[2-5] it is difficult to determine the scope of this phenomenon. α effects, however, do appear to be operable in attack of oxy anions (*e.g.*, ClO^-) and hydrazines on Malachite Green[3,4] and on phenylacetates[2,6] and addition of peroxide to benzonitrile.[7] Although it has been claimed[8] that an α effect exists for a simple SN2 displacements, recent evidence contradicts this assertion.[3] Other reactions for which the α effect may exist include Michael addition of peroxides,[9,10] aromatic nucleophilic displacement,[4,11] and bisulfite addition to carbonyl groups and to oximes.[12]

Although many explanations have been advanced to account for the enhanced reactivity of these nucleophiles, none appears to be entirely satisfactory. These explanations include polarizability of the transition state,[7] enhanced product stability,[4,13] intramolecular general base catalysis,[4,14] and lone pair–lone pair repulsion with associated energy level splitting.[15,16] The first three mechanisms have been discussed by Dixon and Bruice[4] who have concluded that other factors must be involved. A major flaw in the explanation based upon lone pair–lone pair repulsion is the assumption that energy-level splitting necessarily raises the energy of the highest occupied molecular orbital. Highly accurate all-electron quantum chemical calculations and associated thermodynamic analysis show that, in the case of ClO^-, the ionization potential is 2.2 ± 0.4 eV,[17] whereas the value for O^- is 1.478 ± 0.002 eV[18] and for Cl^- is 3.613 ± 0.003 eV[19] (Chart I).

CHART I



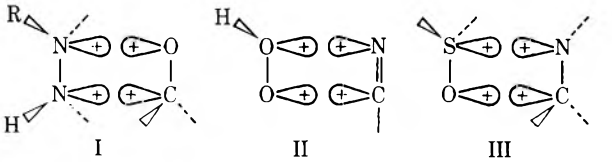
It is clear that simple application of orbital splitting cannot account for the α effect of ClO^- but it is not apparent whether this is a unique situation.[20] In any case, it is obvious that other explanations must be considered.

Any general theory of the α effect must include an explanation of two facts: (1) the rate effect cannot be accounted for solely by a consideration of product stabilities[4] (*i.e.*, an interaction must exist in the transition state which is absent in both reactants and products); (2) the α effect has only been definitely observed for attack of nucleophiles on substrates with π bonding. All previous theories are unable to explain one or both of these phenomena.

We wish to offer an explanation based on the occurrence of an orbital interaction in the transition state which is absent in both reactants and products. This model accounts for the fact that the α effect is only observed for substrates containing π orbitals and explains rate enhancements greater than predicted on the basis of product stabilities.

Zimmerman[21] has devised a method of analyzing orbital interactions in transition states. He has shown that cyclic transition states may be classified into two types. Hückel transition states are characterized by an even number (including zero) of sign inversions between adjacent orbitals in a ring. These transition states exhibit marked stability with [4n + 2] electrons. In contrast, Möbius transition states with an odd number of nodes between orbitals show analogous stability for 4n electrons. Photochemical reactions, of course, show opposite tendencies. Although this approach is not subject to rigorous quantitation, its success has been well documented.[21]

Using this approach we may analyze the transition states for α effect nucleophiles and non α effect nucleophiles. For example, in addition to a carbonyl group by hydrazine, a 6-electron aromatic transition state may be invoked (I). An analogous transition state may be envisioned for peroxide addition to benzonitrile (II) and bisulfite addition to oximes (III). It will be



I II III

(1) (a) J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, **84**, 16 (1962). (b) For a recent review of the α effect, see N. J. Fina and J. O. Edwards, *Int. J. Chem. Kin.*, **5**, 1 (1973).

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(4) J. E. Dixon and T. C. Bruice, *J. Amer. Chem. Soc.*, **93**, 3248, 6592 (1971).

(5) R. F. Pratt and T. C. Bruice, *J. Org. Chem.*, **37**, 3563 (1972).

(6) W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, **82**, 1778 (1960).

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(11) J. F. Bunnett, *J. Amer. Chem. Soc.*, **79**, 5969 (1957).

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(13) J. Hine and R. D. Weimar, *J. Amer. Chem. Soc.*, **87**, 3387 (1965).

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(15) J. D. Aubort and R. F. Hudson, *Chem. Comm.*, 937 (1970).

(16) G. Klopman, K. Tsuda, J. B. Louis, and R. E. Davis, *Tetrahedron*, **26**, 4549 (1970).

(17) P. A. G. O'Hare and A. C. Wahl, *J. Chem. Phys.*, **54**, 3770 (1971).

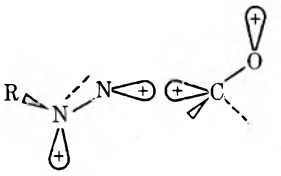
(18) R. S. Berry, J. C. Mackie, R. L. Taylor, and R. Lynch, *J. Chem. Phys.*, **43**, 3067 (1965).

(19) R. S. Berry and C. W. Reimann, *J. Chem. Phys.*, **38**, 1540 (1963).

(20) Although these energies are obtained from calculations on isolated molecules and thus may not be applicable to solutions, it should be realized that the original proposal of orbital splitting suffers from the same defect.[15,16]

(21) H. E. Zimmerman, *Accounts Chem. Res.*, **4**, 272 (1971).

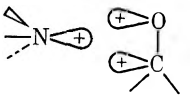
noted that we are proposing cyclic transition states for formally noncyclic reactions. The extra stability of these transition states over the corresponding acyclic transition states (*e.g.*, IV) is, of course, due to the



IV

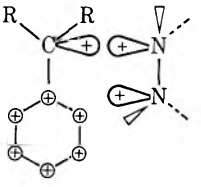
aromatic character of this 6-electron cyclic array. Although a cyclic transition state clearly is entropically disfavored, we may estimate the magnitude of the entropy change on ring formation by a comparison of the model compounds butane and cyclobutane. For these compounds at 300°K, the entropy difference of these molecules is only 10.73 eu or 3.2 kcal/mol.[22] It is reasonable to suppose that the extra stability of an aromatic transition state more than compensates for this entropic loss.[23]

Non-α-effect nucleophiles, on the other hand, cannot react through aromatic transition states similar to I–III and must react through acyclic transition states such as IV. Any interaction of a single orbital from the nucleophile with both orbitals of the π bond would produce a transition state such as V which is antiaromatic as it has only 4 electrons.



V

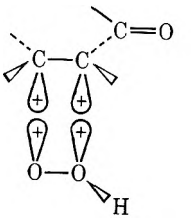
The occurrence of an α effect on the addition of nucleophiles to Malachite Green may be explained similarly. Treating Malachite Green as a substituted benzyl cation, an orbital arrangement such as VI may



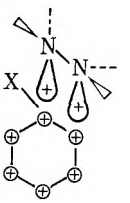
VI

be drawn which has 10-π electrons and is therefore aromatic. Michael addition of peroxides and aromatic nucleophilic substitutions may be treated by drawing structures analogous to I and VI, respectively, such as VII and VIII.

Other reactions for which α effects have been observed are subject to related analysis. Although this treatment is apparently successful in explaining the



VII



VIII

enhanced nucleophilicities of certain species, a definitive experimental proof remains to be produced.

Acknowledgment.—Both J. F. L. and R. M. P. wish to acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

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RECEIVED MAY 22, 1973

(22) D. R. Stull, E. F. Westrum, Jr., and G. C. Sinke, "The Chemical Thermodynamics of Organic Compounds," Wiley, New York, N. Y., 1969.

(23) The nearly ubiquitous success of the Woodward–Hoffman rules indicates that the extra stability of these transition states is quite large.[24] For the pyrolysis of *cis*-3,4-dimethylcyclobutene, the extra stability is $\geq$15 kcal/mol.[25] Similar conclusions have been reached by Hsu, *et al.*,[26] who performed *ab initio* SCF and CI calculations on the potential surfaces of cyclobutene, butadiene, and the corresponding electrocyclic transition states.

(24) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970.

(25) J. I. Brauman and W. C. Archie, Jr., *J. Amer. Chem. Soc.*, **94**, 4262 (1972).

(26) K. Hsu, R. J. Buenker, and S. D. Peyerimhoff, *J. Amer. Chem. Soc.*, **93**, 2117 (1971); **93**, 5005 (1971); **94**, 5639 (1972).

The Reaction of Aryl Nitrones with Thionyl Chloride or Phosgene

Summary: Aryl nitrones react with thionyl chloride or phosgene to yield the corresponding *o*-chloroaniline hydrochlorides.

Sir: In the course of our investigations of aryl nitrones the immediate formation of a copious yellow precipitate was observed upon addition of a molar equivalent of thionyl chloride or phosgene to α,*N*-diphenylnitrone (Ia) dissolved in a minimum amount of benzene at room temperature. The precipitate was purified by sublimation [150° (760 Torr)] yielding a white crystalline substance, the mass spectrum of which exhibited a base peak at *m/e* 215. Elemental analysis indicated a composition of $C_{13}H_{11}Cl_2N$. The ir spectrum, measured as both Nujol and Fluorolube mulls, exhibited strong absorptions at 3.55 and 3.85 μ and medium absorptions at 4.28 and 5.03 μ, all of which have been shown to be characteristic of protonated nitrogen compounds.[1]

The reaction product was thus indicated to be the hydrochloride of benzylidene-*o*-chloroaniline (IIa), a fact confirmed by comparison with an authentic sample prepared according to a method described in the literature.[2] Similar analysis of the residue left after sublimation of the reaction mixture indicated the presence of a small amount of benzylidene-*p*-chloroaniline hydrochloride (IIa′).

This represents a new and interesting reaction route for nitrones. Previous investigations of the reaction of nitrones with acid chlorides (*e.g.*, $POCl_3$, PCl_3) have shown only rearrangement of the nitrone to the corresponding amide.[3]

The closest analogy to the presently reported system is that of aromatic amine oxides with acid chlorides; Meisenheimer reported[4] that quinoline *N*-oxide reacted with acid chlorides to yield 2- and 4-chloroquinoline.

(1) K. Nakanishi, "Infrared Absorption Spectroscopy—Practical," Holden-Day, San Francisco, Calif., 1964, pp 39–45.

(2) O. Fischer and P. Neber, *Ber.*, **45**, 1094 (1912).

(3) J. Hamer and A. Macaluso, *Chem. Rev.*, **64**, 489 (1964).

(4) J. Meisenheimer, *Ber.*, **59**, 1848 (1926).

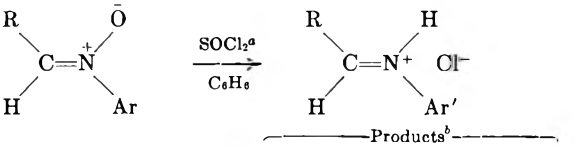
Later work has expanded upon this observation.[5] Indeed, the present work indicates a significant similarity in the chemistry of these two classes of compounds (aromatic amine oxides and aromatic nitrones) which has previously been neglected.[6]

To test the generality of this reaction, a number of other nitrones were synthesized[7] and allowed to react with thionyl chloride or phosgene. These include α-styryl-*N*-phenylnitrone (Ib), α-4-nitrophenyl-*N*-phenylnitrone (Ic), α-styryl-*N*-4-methylphenylnitrone (Id), and α-phenyl-*N*-4-chlorophenylnitrone (Ie). The results are listed in Table I.

The applicability of this reaction as a general, regioselective method for the synthesis of *o*-chloro aromatic imines (and by hydrolysis, the corresponding amines) promises to be quite exceptional. Three steps are involved: (1) reduction of the appropriate nitro compound to the hydroxylamine using Zn/NH_4Cl in aqueous ethanol; (2) condensation of the hydroxylamine with the aldehyde yielding the nitrone; (3) treatment of the nitrone with thionyl chloride or phosgene. In the examples cited each of these steps proceeds rapidly and in high yield. Typically the overall time for the three steps is 2–3 hr, the latter requiring only about 15 min.

Studies are currently in progress to obtain evidence for the mechanism of the above reactions of aryl nitrones and to investigate analogous reactions of compounds containing the –X=N—O grouping (*e.g.*, where X = N).

TABLE I



Reactants			Products[b]		
Compd	R	Ar	Compd	Ar′	Isolated yield, %
			IIa	$2\text{-}ClC_6H_4$	81
Ia	C_6H_5	C_6H_5			
			IIa′	$4\text{-}ClC_6H_4$	6
			IIb	$2\text{-}ClC_6H_4$	71
Ib	C_6H_5CHCH	C_6H_5			
			IIb′	$4\text{-}ClC_6H_4$	3
			IIc	$2\text{-}ClC_6H_4$	82
Ic	$4\text{-}NO_2C_6H_4$	C_6H_5			
			IIc′	$4\text{-}ClC_6H_4$	*c*
Id	C_6H_5	$4\text{-}CH_3C_6H_4$	IId	$2\text{-}Cl\text{-}4\text{-}CH_3C_6H_3$	91
Ie	C_6H_5	$4\text{-}ClC_6H_4$	IIe	$2,4\text{-}Cl_2C_6H_3$	92

[a] No significant differences in yield were observed when phosgene was used instead of thionyl chloride. [b] The structure of each product was determined by comparison of its spectral and physical properties with those of an authentic sample prepared from the known imine. [c] Trace amounts of this material were noted in the crude product but were not isolated. Slight heating was also required for the initiation of this reaction.

(5) T. Ochiai, "Aromatic Amine Oxides," Elsevier, Amsterdam, The Netherlands, 1967, pp 247–339.

(6) In a comparison of aromatic amine oxides with nitrones, reactions involving the carbon–nitrogen double bond should be substantially different, as in aromatic amine oxides the carbon–nitrogen double bond is intimately involved in the aromatic sextet of electrons. However, reactions involving both classes of compounds where they behave as nucleophiles should proceed in similar fashion.

(7) O. H. Wheeler and P. H. Gore, *J. Amer. Chem. Soc.*, **78**, 3363 (1956).

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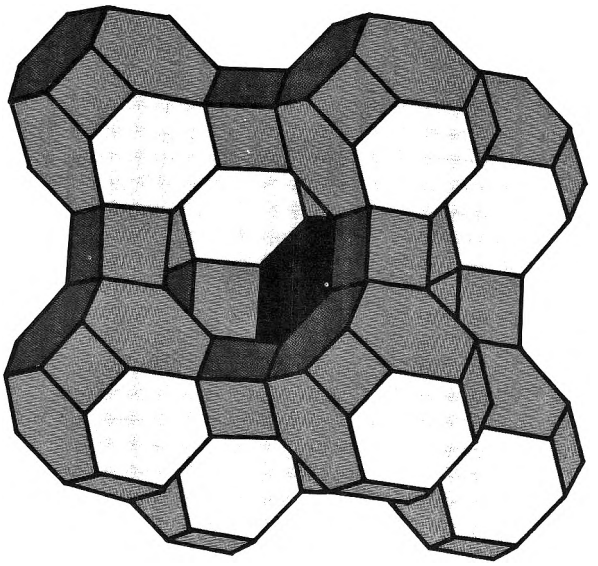

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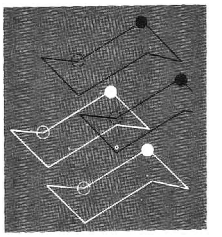

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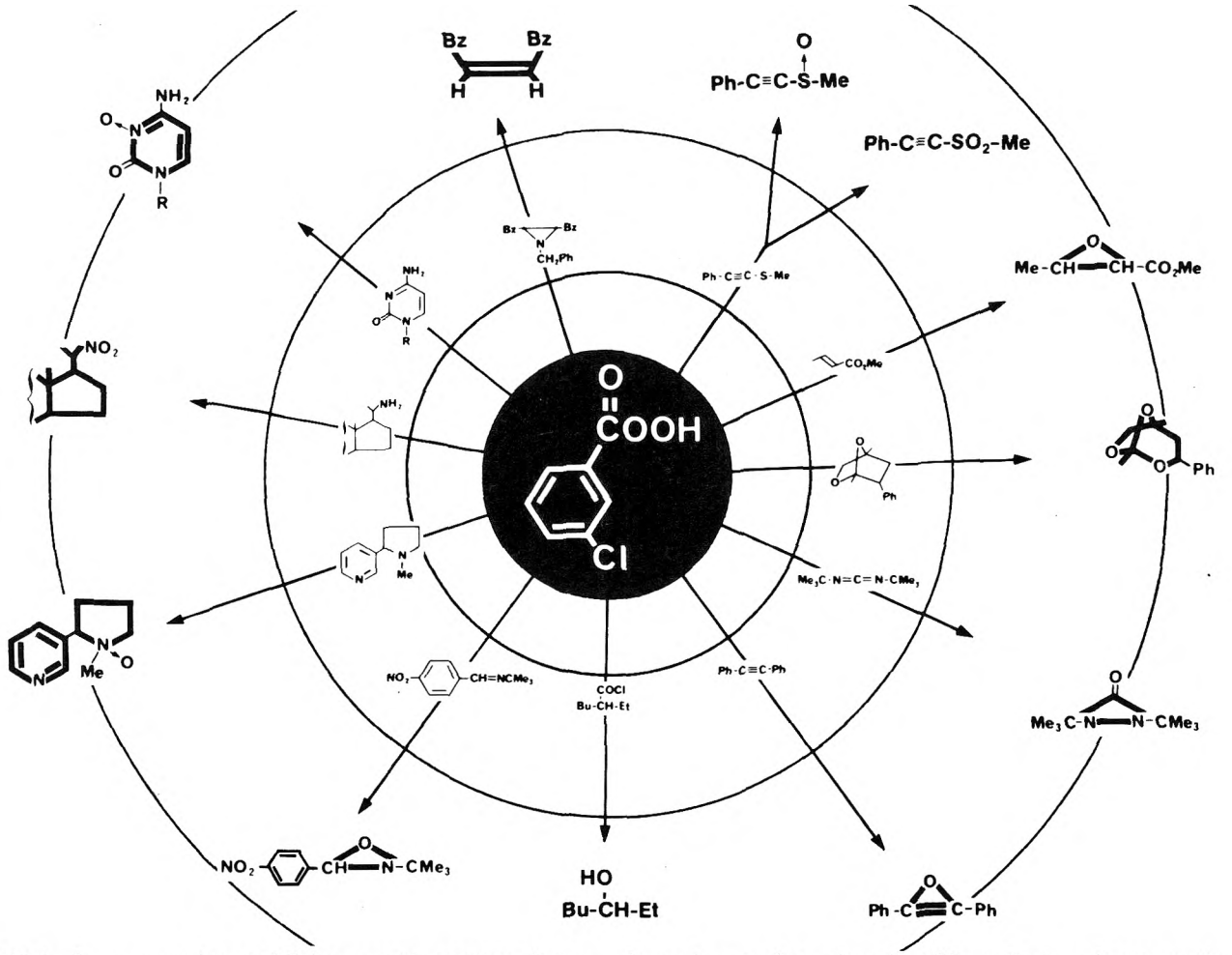
m-CHLOROPEROXYBENZOIC ACID



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 $\alpha.\beta$-unsaturated esters are smoothly oxidized to **epoxides** in nigh yields. In nonconjugated dienes, selective epoxidation occurs in the more substituted double bond. Disubstituted acetylenes can be oxidized to **oxirenes** which break down to ketones, carboxylic acids, or esters depending on the reaction conditions. Like olefins, imines are oxidized to the corresponding **oxaziranes**.

m-CPBA is an excellent reagent for the Baeyer-Villiger oxidation of ketones to **esters**, such as acetylcyclanes and acetophenones. Related to this reaction is the conversion of acid chlorides to **alcohols** in which -OH replaces -COCl. For example, 3-heptanol was obtained in 73% overall yield from 2-ethylhexanoyl chloride.

Primary amines can be converted to **nitroalkanes**, and the yields decrease in the order *tert*-alkyl > *sec*-alkyl > *n*-alkyl. Secondary amines give **nitroxide radicals**, whereas tertiary amines afford the **N-oxides**. 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. Uracil, thymine, and guanosine and their derivatives gave ring-cleavage products. N-substituted aziridines are presumably oxidized to the corresponding N-oxides. This reaction is successfully used in the stereospecific **deamination** of N-alkylaziridines to olefins.

Sulfides can be selectively oxidized to **sulfoxides** or **sulfones** in excellent yields, even in the presence of amine functions, or carbon-carbon double and triple bonds. Some diaziridinones have been prepared from carbodiimides, and some **ortho esters** from ketals.

Space does not allow us to list the numerous references portraying the uses of m-chloroperoxybenzoic acid. **Please write for a detailed data sheet.**

C6270-0 **m-Chloroperoxybenzoic acid,** tech., 85% **25g $8.00; 100g $23.50; 1kg $150.00**

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