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VOLUME 36, NUMBER 15 JULY 30, 1971

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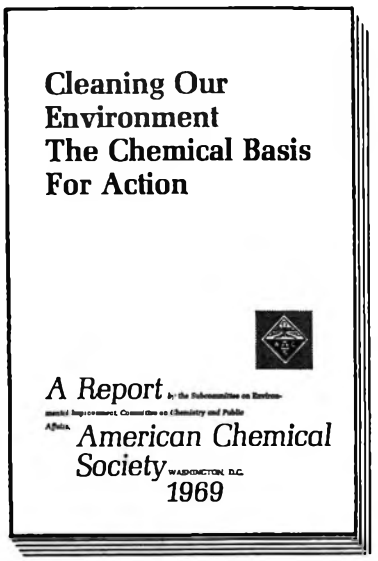

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THE JOURNAL OF Organic Chemistry®

VOLUME 36, NUMBER 15

JULY 30, 1971

Synthesis Studies Relating to Guaiane Sesquiterpenes

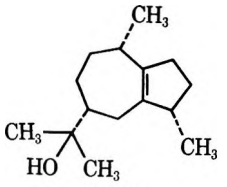
JAMES A. MARSHALL* AND ANDREW E. GREENE[1]

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

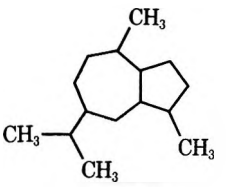
Received December 22, 1970

Acetolysis of the methanesulfonate derivative of 7a-hydroxymethyl-5,6,7,7a-tetrahydroindan (**5**) proceeds smoothly to give the expected hydroazulenic homoallylic acetate **6**. Stereoselective methods for the synthesis of methyl-substituted homologs of carbinol **4** are discussed. One of these entails ozonolysis of the benzyl ether of 10-hydroxymethyl-1,9-octalin (**29**) followed by aldol cyclization of the resulting keto aldehyde. Reductive deconjugation of this aldol product proceeds stereoselectively to give the hydrindanol derivative **31** in which the angular carbinyl and the newly introduced carbinyl center are cis related. This point was established by cyclization of the corresponding diol to the tricyclic ether **34** *via* the monomesylate derivative.

The sesquiterpene alcohol guaiol was one of the first authentic naturally occurring hydroazulenes to be structurally elucidated.[2] It also represents the structural prototype of the guaiane family of sesquiterpenes.[3] Despite its apparent simplicity, guaiol presents a number of difficult synthesis problems. Foremost of these is the general need for stereochemically unambiguous routes to asymmetrically substituted hydroazulenes. In this report we present some preliminary studies relating to this problem which serve to define guidelines for future synthetic work.

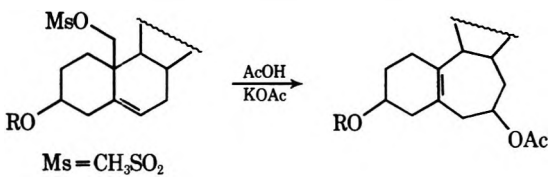


guaiol



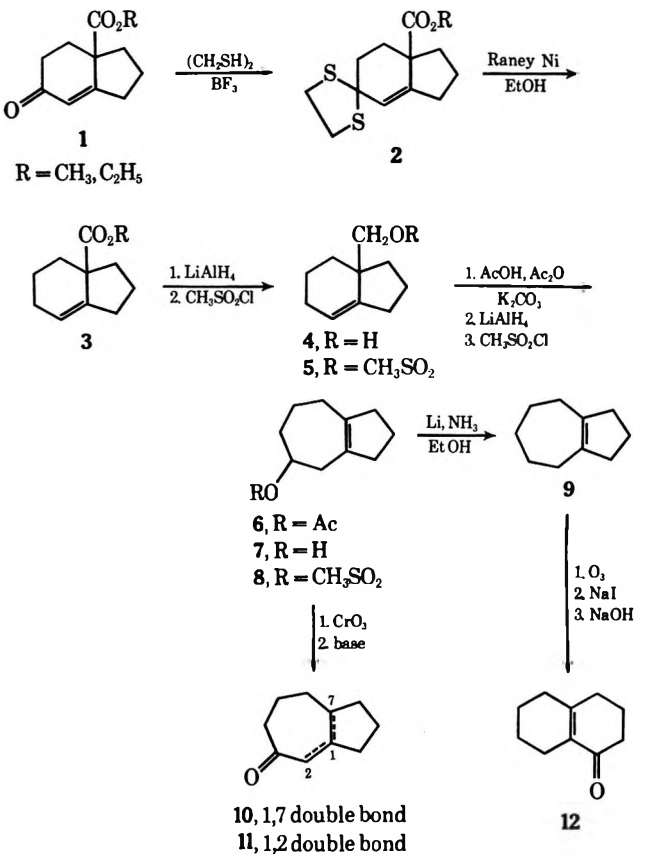
guaiane

The synthetic route that we chose to explore in these studies is based on the work of Tadanier[4] who found that C-19 functionalized Δ^5 steroids of the type depicted below undergo the indicated rearrangement upon acetolysis in a buffered medium. Our initial goal was to examine this rearrangement–solvolysis reaction in the hydrindan system **5** in order to determine its applicability to hydroazulene synthesis. Chart I summarizes our findings.



Ms = CH_3SO_2

CHART I



(1) National Institutes of Health Predoctoral Fellow, Institute of General Medical Sciences, 1967–1970.

(2) H. Minato, *Tetrahedron Lett.*, 280 (1961).

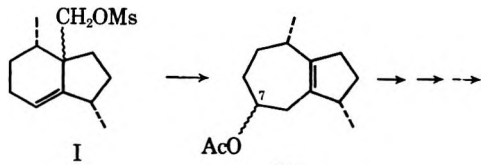
(3) *Cf.* T. Nozoe and S. Itô in "Fortschritte der Chemie Organischer Naturstoffe," L. Zechmeister, Ed., Springer-Verlag, Vienna, 1961, pp 52–61; P. de Mayo, 'Mono and Sesquiterpenoids," Interscience, New York, N. Y., 1959, pp 241–262.

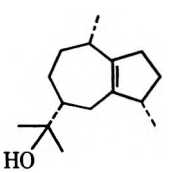
(4) J. Tadanier, *J. Org. Chem.*, **31**, 3204 (1966).

The hydrindanone **1** was prepared *via* base-catalyzed annelation of the commercially available mixture of the methyl and ethyl esters of cyclopentanone-2-carboxylate[5] with methyl vinyl ketone. Desulfurization of the thioketal derivative **2** with W-2 Raney nickel afforded the unsaturated ester mixture **3**. The experimental conditions for this step had to be carefully defined as prolonged heating effected reduction of the double bond, and insufficient Raney nickel or shorter reaction times led to recovery of starting material. Reduction with lithium aluminum hydride yielded the alcohol **4**, an easily purified substance, in 78% overall yield. Solvolysis of the methanesulfonate derivative **5** under the conditions of Tadanier[4] gave the hydroazulenic acetate **6** in nearly 80% yield. The structure of this product was ascertained through its conversion to the hydrocarbon **9** *via* hydrogenolysis of the methanesulfonate derivative **8** with lithium in ammonia and subsequent ozonolysis, followed by aldol cyclization of the resulting 1,5-cyclodecanedione to the known octalone **12**.[6] This sequence establishes the hydroazulenic carbon skeleton and places the double bond. The location of the acetoxyl group was confirmed by oxidation of the corresponding alcohol **7** with Collins' bispyridinechromium(VI) oxide reagent[7] to an unsaturated cycloheptanone **10** which yielded the conjugated isomer **11** upon treatment with base or acid.

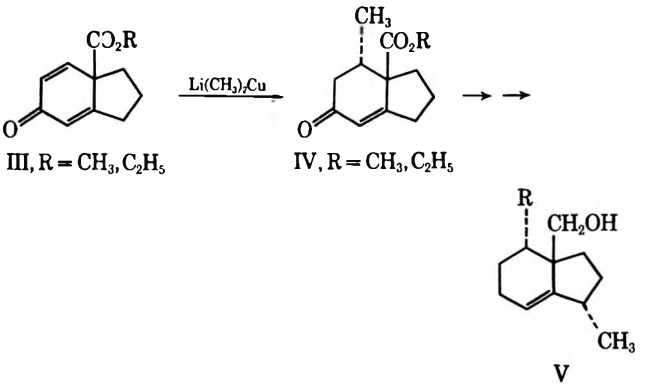
Having established the feasibility of the hydrindan rearrangement route (**5** → **6**) to hydroazulenes, we next turned our attention to the synthesis of a suitable intermediate for subsequent conversion to guaiol along those lines. It should be noted at this point that one intrinsic advantage of the above hydrindan rearrangement route is the opportunity for stereochemical control through the use of conformationally defined cyclohexane derivatives as intermediates with subsequent conversion to the conformationally ambiguous hydroazulene system[8] being effected under nonequilibrating conditions.

Since our synthetic approach called for the final conversion of the acetoxyl substituent in the solvolysis product **6** to the isopropylol substituent of guaiol, we ultimately required a hydrindan such as I for our intended synthesis. The important feature of this intermediate is a cis relationship between the two methyl substituents. At this point we were not concerned with the relative stereochemistry of the angular carbinyl grouping, as this center becomes trigonal in the rearrangement product II. Of course, the relative stereochemistry of the carbinyl carbon (C-7) in acetate II would be determined by the angular carbinyl orientation in I, and this relationship could determine our eventual choice of methodology for introduction of the isopropylol substituent.



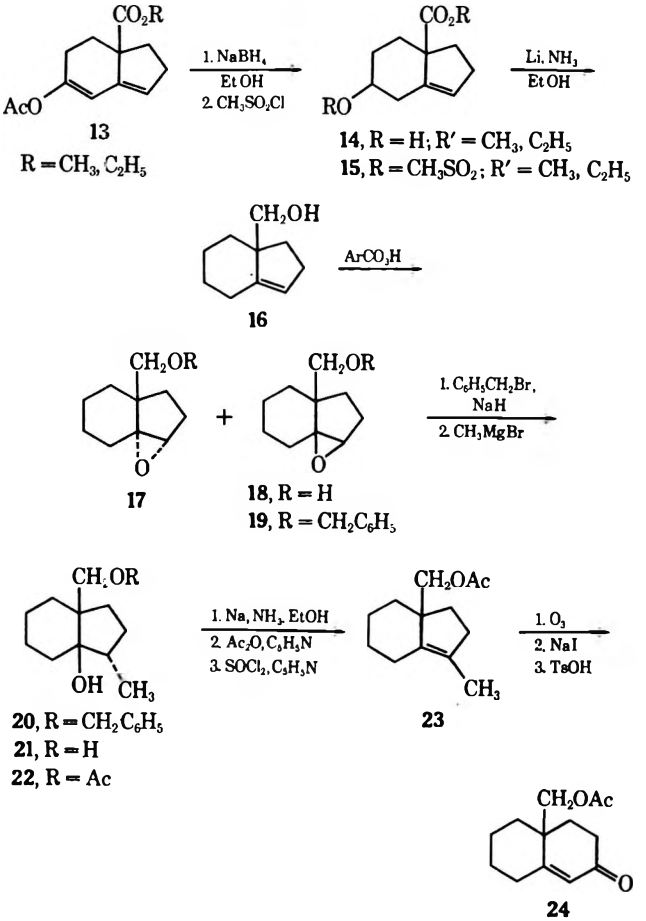


In preliminary experiments we were able to establish that the addition of lithium dimethylcopper to the dienone ester III proceeds in a highly selective fashion to give the enone IV with trans-related methyl and carboxyl groups.[9] In light of this finding we directed our attention to the synthesis of the intermediate V



(R = CH_3). Our initial efforts in this direction (Chart II) were carried out on the demethyl analog **1** of enone IV.

CHART II



(5) Secured fron the Aldrich Chemical Co., Milwaukee, Wis.

(6) A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.*, **75**, 5360 (1953).

(7) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(8) *Cf.* J. B. Hendrickson, *Tetrahedron*, **19**, 1387 (1963); M. Hanack, "Conformation Theory," Academic Press, New York, N. Y., 1965, p 158 ff; E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 206 ff.

(9) A. E. Greene, unpublished results.

Reduction of the enol acetate derivative **13** (mixture of ethyl and methyl esters) of enone **1** with sodium borohydride afforded the homoallylic alcohol **14**. Hydrogenolysis of the derived methanesulfonate **15** with lithium in ammonia–ethanol proceeded with concomitant reduction of the ester grouping to give the unsaturated alcohol **16**. We expected the hydroxyl function of this intermediate to exert a cis-directing effect on the epoxidation of olefin **16** under appropriate conditions[10] to afford the cis isomer **18**. In fact this was found to be the case when the reaction was carried out at low temperature in chloroform or chloroform–methylene chloride (Table I). Under comparable conditions

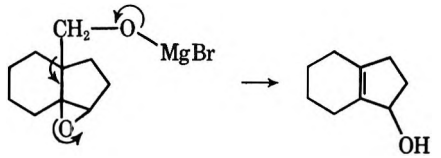
TABLE I
EPOXIDATION OF HOMOALLYLIC ALCOHOL **16** WITH *m*-$ClC_6H_4CO_3H$

Solvent	Temp, °C	β (18)/α (17)[a]
THF–H_2O[b]	0	15/85
DME–H_2O[b]	0	25/75
Ether	25	33/67
Acetonitrile	0	50/50
Cyclohexane	12	67/33
Chloroform	0	75/25
	−20	80/20
Chloroform–methylene chloride	−78	85/15
Chloroform[c]	0	30/70

[a] The ratio was determined by gas chromatography. [b] Buffered with K_2HPO_4. [c] Epoxidation of the acetate of **15**.

the acetate derivative of alcohol **16** afforded mainly (see Table I) the trans epoxy acetate derivative **17** (R = Ac).[9] Interestingly, the epoxidation of unsaturated alcohol **16** showed a marked solvent dependence even with aprotic solvents.

The requisite trans methyl grouping was introduced *via* treatment of the benzyl ether derivative **19** of epoxide **18** with methylmagnesium bromide in refluxing tetrahydrofuran to give the alcohol **20**. When the epoxy alcohol **18** was similarly treated, a fragmentation reaction took place leading to the alcohol VI.[9] The

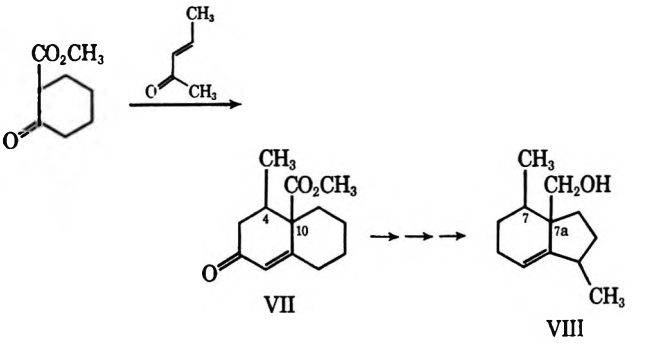


VI

same alcohol was produced upon similar treatment of the trans epoxy acetate **17** (R = Ac).[9]

At this point our projected synthesis of the trans alcohol V (R = H) took an unexpected turn. We had hoped that the hydroxy acetate **22**, secured from alcohol **20** *via* hydrogenolysis with sodium in ammonia–ethanol followed by selective acetylation of the resulting diol **21**, would undergo a specific trans dehydration leading to the desired trisubstituted olefin.[11] However, our efforts to effect this conversion were to no avail. The tetrasubstituted olefin **23** was the only detectable product of various dehydration attempts. The structure of this material was confirmed through its conversion, *via* ozonolysis and acid-catalyzed aldol cyclization, to the known acetoxy enone **24**.[12]

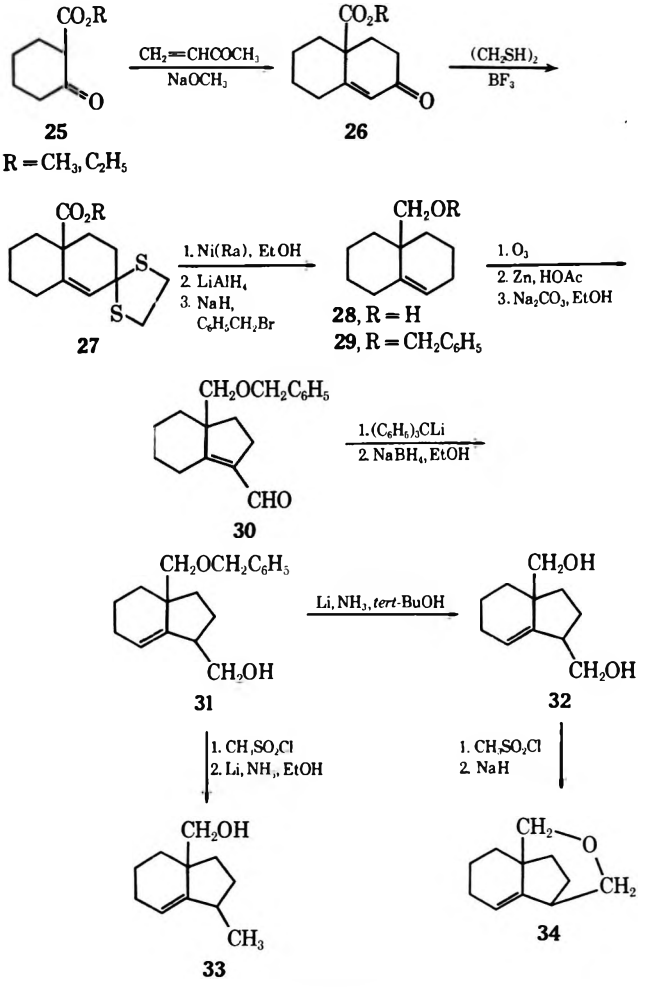
In view of the foregoing results we decided to abandon our efforts to prepare the alcohol V (R = CH_3) and study instead the synthesis of the all-cis isomer VIII along the general lines depicted below. The stereo-



VII VIII

chemical groundwork for the C-4/C-10 relationship in VII (and thus the C-7/C-7a relationship in VIII) had been established by some of our earlier work.[13] We therefore needed only to devise a method for introducing the second *cis*-methyl group. For studies on this point (Chart III) we employed as a model com-

CHART III



(10) H. B. Henbest, *Proc. Chem. Soc.*, 159 (1963).

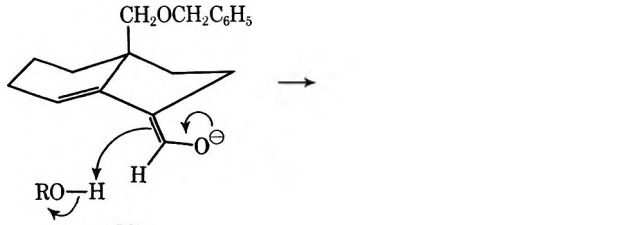
(11) *Cf.* J. A. Marshall, N. Cohen, and A. R. Hochstetler, *J. Amer. Chem. Soc.*, **88**, 3408 (1966); J. A. Marshall and A. R. Hochstetler, *ibid.*, **91**, 684 (1969).

(12) T. M. Warne, Jr., unpublished results.

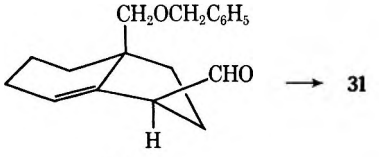
(13) T. Warne, Jr., Ph.D. Dissertation, Northwestern University, 1970.

pound the methyl vinyl ketone adduct **26** of the commercially available mixture of methyl and ethyl esters of cyclohexanone-2-carboxylate (**25**).[5] Our projected guaiol synthesis would of course require the aforementioned methyl propenyl ketone Michael-aldol adduct VII as the starting material.

The known homoallylic alcohol **28**[14] was prepared *via* desulfurization of the thioketal derivative **27** and reduction of the resulting mixture of methyl and ethyl esters. The benzyl ether derivative **29**, obtained through treatment of alcohol **28** with sodium hydride and benzyl bromide, was subjected to ozonolysis followed by a reductive work-up. The resulting keto aldehyde cyclized upon stirring with ethanolic sodium carbonate to give the unsaturated aldehyde **30**. Conversion to the homoallylic alcohol **31** was effected by addition of the enolate, secured *via* treatment of aldehyde **30** with triphenylmethyllithium, to ethanolic sodium borohydride. The indicated stereochemical outcome was predicted on the assumption that protonation of the enolate **30a** by ethanol would occur from the less hindered face of the trigonal α position to give the β,γ-unsaturated aldehyde **30b**, which would then be reduced by sodium borohydride before epimerization could take place. In fact, a 9:1 mixture of alcohol **33** and its presumed epimer was obtained from this sequence. The stereochemistry of alcohol **31** was confirmed through hydrogenolysis of the benzyl ether using lithium in ammonia–*tert*-BuOH and cyclization of the resulting diol **32** to the tricyclic ether **34** *via* basic treatment of the monomesylate derivative. The desired methyl compound **33** was secured from alcohol **31** by hydrogenolysis of the methanesulfonate derivative with lithium in ammonia–ethanol.



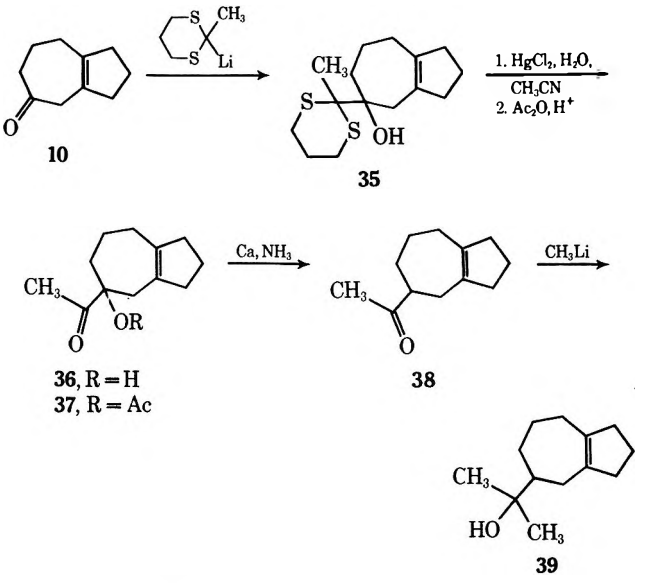
30a



30b → **31**

In considering the applicability of the hydrindanylcarbinol rearrangement to a synthesis of guaiol we had to provide for some means of introducing the isopropylol substituent at the appropriate cycloheptane ring position. Our initial plan was to conduct the solvolysis–rearrangement reaction (*e.g.*, **5** → **6**) in liquid HCN containing KCN as a buffer, whereupon the cyano counterpart of the hydroazulenic acetate **6** might have been formed directly. Unfortunately initial experiments along these lines looked unpromising.[9] Likewise, attempts to prepare organometallic derivatives[15] and efforts to effect displacement reactions[16] on the appropriate halo compound proved unsuccessful. We were thus forced to consider less direct routes to the requisite isopropylol compound (*e.g.*, **39**). A successful scheme which evolved from our preliminary studies is outlined in Chart IV.

CHART IV



The β,γ-unsaturated ketone **10** condensed with the lithio derivative of 2-methyl-1,3-dithiane[17] to give alcohol **35**. This product could not be obtained free of starting material despite the use of excess organolithium reagent (enolate formation?). Fortunately the crude product contained none of the conjugated ketone **11** and the mixture could thus be recycled. Hydrolysis of the thioketal **35** proceeded smoothly to give the ketol **36**. Acetylation followed by hydrogenolysis with calcium in ammonia afforded the ketone **38**, provided the excess calcium was destroyed with bromobenzene[18] before work-up. Otherwise, further reduction of ketone **38** to the corresponding alcohol took place. Treatment of this ketone with methyllithium gave the desired alcohol **39**.

The work described in this report provides a reasonable basis for a potential synthesis of guaiol. Further work toward the end is in progress.

Experimental Section[19]

7a-Hydroxymethyl-5,6,7,7a-tetrahydroindan (4).—A solution of 5.28 g (*ca.* 26 mmol) of keto ester **1** (methyl, ethyl mixture), 5.8 ml (68.9 mmol) of 1,2-ethanedithiol, and 1.4 ml (11.0 mmol) of boron trifluoride etherate in 12 ml of acetic acid was stirred at 0° for 2 hr and stored at 5° for 8 hr. The product was isolated with ether and the residual ethanedithiol was removed under high vacuum affording 7.36 g of thioketal **2** (methyl, ethyl

(14) J. W. Rowe, A. Melera, D. Arigoni, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **40**, 1 (1957).

(15) *Cf.* (a) C. H. Heathcock and T. R. Kelly, *Tetrahedron*, **24**, 1801 (1968); (b) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, pp 618–619, 711–712.

(16) *Cf.* H. Normant, *Bull. Soc. Chim. Fr.*, 791 (1938); *Angew. Chem., Int. Ed. Engl.*, **6**, 1046 (1967); ref 15b, pp 297–298, 696.

(17) E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1075 (1965); E. J. Corey and D. Crouse, *J. Org. Chem.*, **33**, 298 (1968); D. Seebach, N. R. Jones, and E. J. Corey, *ibid.*, **33**, 300 (1968).

(18) E. S. Rothman and M. E. Wall, *J. Amer. Chem. Soc.*, **79**, 3228 (1957).

(19) Reactions were carried out under an atmosphere of nitrogen. The isolation procedure involved adding the reaction mixture to water or saturated brine followed by thorough extraction with the specified solvent. Anhydrous magnesium sulfate or potassium carbonate was used to dry the combined extracts and the solvent was subsequently removed on a rotary evaporator under reduced pressure. Microanalyses were performed by Microtech Inc., Skokie, Ill.

mixture): λ_{max}^{film} 5.80, 6.90, 7.82, 8.00, 8.45, 9.28, 9.73, 11.45, and 11.72 μm.

The above material was stirred with 120 ml (*ca.* 72 g) of W-2 Raney nickel in 1.7 l. of ethanol at reflux for 55 min. The cooled mixture was filtered and concentrated by distillation and the product was isolated with ether, affording 4.21 g of ester **3** (methyl, ethyl mixture): λ_{max}^{film} 5.81, 6.90, 7.69, 8.08, 8.55, 9.25, 9.72, 10.50, and 11.55 μm. Longer reflux periods afforded material contaminated with the product of double bond reduction.

The above ester mixture in 50 ml of ether was added to a solution of 2.50 g (65.8 mmol) of lithium aluminum hydride in 300 ml of ether. The mixture was stirred for 8 hr and treated with 5 ml of water and 4 ml of 10% aqueous NaOH. After 1 hr of continued stirring a small amount of anhydrous magnesium sulfate was added and the mixture was filtered, concentrated under reduced pressure, and distilled, affording 3.12 g (*ca.* 78% overall yield) of alcohol **4**, bp 110° (bath temperature) at 0.1 mm: λ_{max}^{film} 3.00, 3.29, 6.85, 9.20, 9.60, 9.75, 10.38, 11.25, and 12.32 μm; $\delta_{TMS}^{CCl_4}$ 5.38 (broad, H-4), and 3.35 ppm (broad, CH_2-OH). The analytical sample, mp 35.5–37°, was prepared by preparative gas chromatography[20] and short-path distillation.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.8; H, 10.3.

Bicyclo[5.3.0]dec-1(7)-en-3-yl Acetate (6).—A stirred solution of 1.30 g (8.6 mmol) of alcohol **4** in 9 ml of pyridine was treated dropwise with 3.9 ml (51.5 mmol) of methanesulfonyl chloride at 0°. After 20 min the mixture was slowly poured into a solution containing 75 ml of pyridine and 10 ml of water at 0°, and the product was isolated with ether, affording 1.88 g (96%) of mesylate **5**: λ_{max}^{film} 3.30, 6.87, 7.38, 8.50, 10.25, 10.58, 11.85, and 12.37 μm; $\delta_{TMS}^{CCl_4\text{-}CDCl_3}$ 5.65 (broad, H-4), 4.05 (CH_2O, AB, J = 10 Hz, $\Delta\nu$ = 11 Hz), and 3.04 ppm (CH_3SO_3).

The above product in 130 ml of a solution prepared from 250 ml of acetic acid, 5 ml of acetic anhydride, and 3.50 g of potassium carbonate (previously heated at reflux overnight) was stirred at reflux for 5 hr.[4] The product was isolated with ether and distilled, affording 1.32 g (83%) of acetate **6**, bp 85° (bath temperature) at 0.1 mm (*ca.* 90% pure according to gas chromatography[21]): λ_{max}^{film} 5.77, 6.91, 7.30, 8.03, 9.74, 10.22, and 10.59 μm; $\delta_{TMS}^{CCl_4}$ 4.75 (broad, H-3), 2.40 and 2.28 (broad, allylic H's), and 1.94 ppm (CH_3CO).

The analytical sample was prepared *via* preparative gas chromatography[20] and short-path distillation.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.1; H, 9.5.

Bicyclo[5.3.0]dec-1(7)-en-3-ol (7).—A solution of 1.32 g (6.8 mmol) of acetate **6** in 25 ml of ether was added dropwise with stirring to a solution of 1.50 g (39.5 mmol) of lithium aluminum hydride in 225 ml of ether. After 3 hr, 3 ml of water and 2.4 ml of 10% aqueous NaOH were added and stirring was continued for 1 hr. A small amount of anhydrous magnesium sulfate was added and the mixture was filtered and distilled, affording 1.02 g (99%) of alcohol **7**, bp 80° (bath temperature) at 0.4 mm (90% pure according to gas chromatography[21]): λ_{max}^{film} 3.00, 6.91, 9.58, 9.77, 9.95, and 10.75 μm; $\delta_{TMS}^{CCl_4}$ 3.65 (broad, H-3), 2.38, and 2.25 ppm (allylic H's). The analytical sample, mp 47.5–49.5°, was secured *via* preparatuve gas chromatography,[20] followed by short-path distillation and sublimation (25° at 0.2 mm).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 79.1; H, 10.6.

Bicyclo[5.3.0]dec-1(7)-ene (9).—A stirred solution of 0.38 g (2.5 mmol) of alcohol **7** in 2.7 ml of pyridine of 0° was treated dropwise with 1.17 ml (15.4 mmol) of methanesulfonyl chloride. After 20 min the mixture was slowly added to a solution of 5 ml of water in 20 ml of pyridine at 0° and the product was isolated with ether, affording 0.33 g (57%) of mesylate **8**: λ_{max}^{film} 6.91, 7.37, 8.34, 8.49, 10.25, 10.55, 10.95, 11.93, and 13.15 μm; $\delta_{TMS}^{CCl_4\text{-}CDCl_3}$ 2.99 ppm (CH_3SO_3).

The above mesylate in 1.7 ml of ethanol was added dropwise to a stirred solution of 0.41 g (59 mg-atoms) of lithium in 30 ml of ammonia at −78°. After 1 hr at −78° and 0.5 hr at −33° (reflux) ethanol was added dropwise to discharge the blue color, followed by solid ammonium chloride. The ammonia was allowed to evaporate through a mercury bubbler and the product was isolated with ether, affording 0.18 g of olefin **9** (55% pure according to gas chromatography[22]): λ_{max}^{film} 6.91, 7.65, 7.82, 8.12, and 9.35 μm: $\delta_{TMS}^{CDCl_3}$ 2.38 and 2.27 ppm (allylic H's).

The analytical sample, bp 70° (bath temperature) at 20 mm, was secured *via* preparative gas chromatography[23] followed by short-path distillation.

Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 88.1; H, 12.1.

Bicyclo[5.3.0]dec-1(7)-en-3-one (10).—A stirred solution of 64 mg (0.42 mmol) of alcohol **7** in 10 ml of methylene chloride was treated with 640 mg (2.48 mmol) of Collins bispyridinechromium(VI) oxide reagent.[7] After 1 hr ether was added and the mixture was washed with aqueous sodium bicarbonate, water, and 10% aqueous HCl, dried over anhydrous potassium carbonate, and distilled, affording 53 mg (84%) of ketone **10**, bp 70° (bath temperature) at 0.05 mm (90% pure according to gas chromatography[21]): λ_{max}^{film} 5.86, 6.00, 6.97, 7.11, 7.49, 7.58, 7.78, 7.99, 8.21, 9.43, 9.80, and 10.08 μm.

The analytical sample was secured *via* preparative gas chromatography,[23] followed by short-path distillation.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.7; H, 9.2.

Bicyclo[5.3.0]dec-1-en-3-one (11).—A stirred mixture containing 120 mg of ketone **10**, comparable to that described above, and 0.25 g of sodium carbonate in 20 ml of methanol and 2 ml of water was heated at reflux for 3.75 hr. The product was isolated with ether, affording material shown by gas chromatography[24] to contain 65% of starting β,γ-unsaturated ketone **10** and 30% of conjugated ketone **11**. The latter component was isolated *via* preparative gas chromatography[23] and short-path distillation (80° at 0.05 mm): λ_{max}^{film} 3.32, 6.03, 6.90, 7.39, 7.98, 8.48, 9.53, 11.47, and 12.05 μm: $\delta_{TMS}^{CCl_4}$ 5.89 ppm (H-2).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.7; H, 9.5.

Treatment of the β,γ-unsaturated ketone **10** with ethanolic oxalic acid (15 mg/ml of 95% ethanol) at 66° for 15.5 hr afforded a mixture containing 51% of starting ketone **10** and 34% of conjugated ketone **11**.

9-Octal-1-one (12).—A solution of 100 mg of crude olefin **9** in 2.5 ml of pentane was treated at −78° with a stream of ozonized oxygen until the appearance of a blue coloration. The excess ozone was allowed to evaporate and the mixture was added to a stirred solution of 0.6 g of NaI and 0.7 ml of acetic acid in 1 ml of methanol at 0°. After 15 min at 0° and 1.5 hr at room temperature the mixture was shaken with aqueous sodium bisulfite and the product was isolated with ether.

The resulting dione (λ_{max}^{film} 5.87 μm) was stirred with 5 ml of 10% aqueous NaOH at 70° for 1.5 hr. The product was isolated with ether and purified *via* preparative gas chromatography,[20] affording the enone **12**: λ_{max}^{film} 6.02, 6.12, 6.88, 6.97, 7.20, 7.39, 7.56, 7.78, 7.91, 8.36, 8.86, 8.99, 9.62, 10.96, and 11.80 μm. This material was identified by spectral and gc comparison with an independently prepared sample.[6]

7a-Hydroxymethyl-2,4,5,6,7,7a-hexahydroindene (16).—A solution of 10.0 g (*ca.* 50 mmol) of keto ester **1**[25] (methyl, ethyl mixture) in 927 ml of ethyl acetate containing 185 μl of 70% perchloric acid and 89 ml of acetic anhydride[26] was allowed to stand for 8 min. The solution was washed with aqueous sodium bicarbonate and the product was isolated with ethyl acetate and distilled, affording 10.8 g (*ca.* 90%) of enol acetate **13**, bp 100° (0.05 mm): λ_{max}^{film} 5.67, 5.80, 6.00, 6.10, 6.94, 7.32, 8.30, 8.95, 9.30, 9.85, and 10.85 μm.

The above product in 250 ml of ethanol was added dropwise to a stirred solution containing 29 g of sodium borohydride in 1.21 l. of ethanol and 188 ml of water at 0°. After 45 min at 0° the mixture was stored at 5° for 35 hr and poured into 200 ml of 10% aqueous NaOH. The product was isolated with ether–benzene, affording 8.6 g (*ca.* 95%) of alcohol **14**: λ_{max}^{film} 3.00, 3.26, 5.80, 5.98, 6.90, 8.45, 9.35, and 9.69 μm.

An 8.0-g sample of the above alcohol in 25 ml of pyridine was stirred at 0° during the addition of 8.3 ml (109 mmol) of methanesulfonyl chloride. After 6 hr at room temperature the stirred

(20) A 13.5 ft × 0.5 in. column of 9% FFAP on 70–80 mesh Chromosorb G was used.

(21) A 22 ft × 0.12 in. column of 4% FFAP on 70–80 mesh Chromosorb G was used.

(22) A 22 ft × 0.12 in. column of 1% Carbowax 20M on 80–100 mesh Chromosorb G was used.

(23) A 13.5 ft × 0.5 in. column of 9% Dow Corning silicone oil 550 on 70–80 mesh Chromosorb G was used.

(24) A 15 ft × 0.12 in. column of 4% Dow Corning silicone oil 550 on 60–70 mesh Chromosorb G was used.

(25) W. G. Dauben, J. W. McFarland, and J. B. Rogan, *J. Org. Chem.*, **26**, 297 (1961).

(26) B. E. Edwards and P. N. Rao, *ibid.*, **31**, 324 (1966).

mixture was cooled to 0° and small chips of ice were added to destroy the excess acid chloride. The product was isolated with ether, affording 8.7 g (*ca.* 80%) of semisolid mesylate **15**: λ_{max}^{film} 3.29, 5.80, 5.98, 6.90, 7.40, 7.92, 8.20, 8.50, 9.10, 9.69, 10.10, 10.35, 11.92, and 13.16 μm.

The above product in 91 ml of ethanol and 48 ml of tetrahydrofuran was added with stirring to a solution of 16.1 g (2.31 g-atoms) of lithium in 1.35 l. of ammonia at −78°. After 1 hr at −78° and 1.5 hr at −33° (reflux) ethanol was added to discharge the blue color and solid ammonium chloride was added to destroy the basic alkoxides. The ammonia was allowed to evaporate through a mercury bubbler and the product was isolated with ether and distilled twice, affording 3.01 g (*ca.* 65%) of alcohol **16**, bp 90° (bath temperature) at 0.07 mm (95% pure according to gas chromatography[27]): λ_{max}^{film} 2.98, 3.28, 6.00, 6.90, 9.57, 9.80, and 12.60 μm; $\delta_{TMS}^{CCl_4-CDCl_3}$ 5.45 (broad, vinylic H) and 3.50 ppm (CH_2OH).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 79.2; H, 10.7.

Epoxidation of Unsaturated Alcohol 16.—A stirred solution of 0.80 g (5.26 mmol) of olefin **16** in 370 ml of chloroform and 75 ml of methylene chloride at −78° was treated with 4.0 g (17.9 mmol) of *m*-chloroperoxybenzoic acid (77% peroxy acid by titration). After 108 hr at −78° the mixture was poured into 10% aqueous NaOH and the product was isolated with chloroform and distilled, affording 0.71 g (80%) of oil, bp 120° (bath temperature) at 0.15 mm, shown to be an 85:15 mixture of the β-epoxide **18** and the α-epoxide **17** by gas chromatography:[27] λ_{max}^{film} 2.90, 6.92, 8.98, 9.52, 9.67, 10.82, 11.68, and 12.60 μm; $\delta_{TMS}^{CCl_4}$ 3.65 (CH_2OH) and 3.40 and 3.20 ppm (carbinyl H's of the α and β-epoxides, respectively).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.2; H, 9.5.

***trans*-3-Methyl-7a-acetoxymethyl-3a,4,5,6,7,7a-hexahydro-*cis*-indan-3a-ol (22).**—A solution of 100 mg (0.60 mmol) of alcohol **18** (15% **17**) in 3 ml of dioxane was added to hexane-washed NaH [from 50 mg (1.2 mmol) of 57% oil dispersion] and the mixture was stirred at reflux for 1 hr. The cooled solution was treated with 0.14 g (0.82 mmol) of benzyl bromide in 2 ml of dioxane and reflux was resumed for 12 hr. The product was isolated with ether and distilled, affording 112 mg (73%) of ether **19**, bp 140° (bath temperature) at 0.1 mm: λ_{max}^{film} 3.30, 6.87, 7.31, 9.05, 11.59, 13.55, and 14.31 μm; $\delta_{TMS}^{CCl_4}$ 7.34 (aromatic H's), 4.55 (benzylic H's), 3.55 (CH_2O, AB, J = 9, $\Delta\nu$ = 26.5 Hz), and 3.09 ppm (carbinyl H).

To 330 mg (1.28 mmol) of epoxide **19**, comparable to that described above, in 18 ml of tetrahydrofuran (THF) was added a solution of methylmagnesium bromide (from 6.6 g of Mg in 60 ml of THF) and the mixture was stirred at reflux for 66 hr. The product was isolated with ether–ethyl acetate and distilled, affording 362 mg of crude alcohol **20**, bp 130° (bath temperature) at 1.5 mm: λ_{max}^{film} 2.95, 3.31, 6.88, 7.31, 9.28, 9.74, 13.55, and 14.30 μm; $\delta_{TMS}^{CCl_4}$ 7.20 (aromatic H's), 4.40 (benzylic H's), 3.60 (–CH_2O– multiplet), and 0.85 ppm (CH_3 doublet, J = 6 Hz).

To a 100-mg sample of the above alcohol in 1 ml of ether and 15 ml of ammonia at −33° (reflux) was added 120 mg of Na. After 1 hr ammonium chloride was added, the ammonia was allowed to evaporate through a mercury bubbler, and the product was isolated with ethyl acetate, affording 70 mg of diol **21** (70% pure according to gas chromatography[27]): λ_{max}^{film} 2.99, 6.85, 7.26, 9.45, and 9.78 μm.

A 400-mg sample of diol **21** comparable to that described above was stirred at room temperature overnight with 14 ml of pyridine and 10 ml of acetic anhydride. The product was isolated with ethyl acetate and distilled, affording 414 mg of white solid, bp 120° (bath temperature) at 0.05 mm. Crystallization from chloroform–hexane afforded 110 mg (24%) of acetate **22**, white needles, mp 104.5–107°: λ_{max}^{KBr} 2.87, 5.84, 6.85, 7.18, 7.30, 7.88, 9.60, 9.88, and 10.18 μm; $\delta_{TMS}^{CCl_4-CDCl_3}$ 4.07 (carbinyl CH_2), 2.05 (CH_3CO), and 0.90 ppm (CH_3 doublet, J = 6 Hz).

A second crop of 54 mg (12%) was obtained.

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.0; H, 10.0.

Dehydration of Alcohol 22.—A solution of 46 mg (0.20 mmol) of alcohol **22** in 1.35 ml of pyridine was stirred at 0° and 0.12 ml of thionyl chloride was added dropwise. After 25 min, the solution was poured onto crushed ice and the product was isolated with ether and distilled, affording 37 mg (87%) of acetate **23** (98% pure according to gas chromatography),[22,27] bp 80° (bath temperature) at 0.03 mm: λ_{max}^{film} 5.75, 6.88, 7.25, 8.08, and 9.60 μm; $\delta_{TMS}^{CCl_4}$ 3.97 (carbinyl CH_2), 1.97 (CH_3CO), and 1.60 ppm (vinylic CH_3).

The same results were obtained when the dehydration was carried out for 1 hr at −30 to −40°.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.8; H, 9.8.

10-Acetoxymethyl-1(9)-octal-2-one (24).—A solution of 37 mg of olefin **23**, comparable to that described above, in 2.5 ml of pentane at −78° was treated with a stream of ozonized oxygen until the solution became blue. The excess ozone was allowed to evaporate and the precipitated ozonide was added to a stirred solution containing 0.3 g of NaI and 0.35 ml of acetic acid in 1 ml of methanol at 0°. After 1 hr at 0° and 1 hr at room temperature, the mixture was shaken with aqueous sodium bisulfite and the product was isolated with ethyl acetate and distilled, affording 30 mg of dione, bp 150° (bath temperature) at 0.1 mm (80% pure according to gas chromatography[27]): λ_{max}^{film} 5.74, 5.84, 6.90, 7.27, 7.35, 8.10, and 9.63 μm.

The above sample was refluxed with 18 mg of *p*-toluenesulfonic acid monohydrate in 12 ml of benzene for 17.5 hr, with removal of water *via* a Dean–Stark trap. The product was isolated with ethyl acetate and distilled (short path), affording 21 mg of enone **24** (85% pure according to gas chromatography[27]): λ_{max}^{film} 3.30, 5.75, 5.98, 6.16, 6.89, 7.29, 8.10, 9.55, 11.53, and 12.92 μm; $\delta_{TMS}^{CCl_4}$ 5.75 (vinylic H), 4.25 (carbinyl CH_2, AB, J = 12, $\Delta\nu$ = 13 Hz), and 2.00 ppm (CH_3CO).

The spectral properties and gas chromatographic behavior of this material were indistinguishable from those of an authentic sample.[12]

10-Hydroxymethyl-1(9)-octalin (28).—To a solution of 55.39 g (*ca.* 0.34 mol) of keto ester **25** (methyl, ethyl mixture) in 108 ml of 0.074 *M* sodium methoxide at −5 to −15° was added dropwise over a period of 3 hr a solution of 23.4 g (0.339 mol) of methyl vinyl ketone in 75 ml of methanol. After addition was complete 10 ml of 1 *M* sodium methoxide was added and the mixture was allowed to reach room temperature. An additional 250 ml of 1 *M* methoxide was then added and, after 12 hr, acetic acid was added to neutralize the base and the product was isolated with benzene and distilled, affording 60.3 g (*ca.* 83%) of keto ester **26**, bp 110–125° at 0.25 mm: λ_{max}^{film} 3.31, 5.79, 5.98, 6.15, 6.92, 7.00, 7.52, 7.75, 7.96, 8.14, 8.27, 8.50, 9.20, 9.72, 9.88, 10.25, 10.67, and 11.65 μm.

A 5.68-g sample of the above keto ester, 5.8 ml of 1,2-ethanedithiol, and 1.4 ml of boron trifluoride etherate in 12 ml of acetic acid was stirred at 0° for 2 hr and kept at 5° for 9 hr. The product was isolated with ether and freed of excess ethanedithiol under vacuum, affording 7.60 g of thioketal **27**: λ_{max}^{film} 3.27, 5.80, 6.95, 7.02, 7.78, 8.00, 8.20, 8.45, 8.89, 9.21, 9.90, 10.15, and 11.62 μm.

The above-described thioketal in 500 ml of ethanol was stirred at reflux with 75 ml (45 g) of W-2 Raney nickel for 2 hr. The cooled mixture was filtered and concentrated by distillation, and the product was isolated with ether and distilled, affording 4.26 g (*ca.* 80%) of ester, bp 90° (bath temperature) at 0.06 mm: λ_{max}^{film} 3.29, 5.78, 6.92, 7.72, 7.91, 8.21, 8.61, 8.83, 9.18, 9.75, 9.98, and 12.35 μm.

The above sample in 50 ml of ether was added to 2.50 g of lithium aluminum hydride in 300 ml of ether with stirring. After 12 hr, 5 ml of water and 4 ml of 10% aqueous NaOH were added and the mixture was stirred for 1 hr, treated with anhydrous magnesium sulfate, and filtered. Distillation afforded 3.49 g (99%) of alcohol **28**, bp 100° (bath temperature) at 0.02 mm, mp 67–68° (lit.[14] mp 69.5–70°): λ_{max}^{KBr} 3.00, 3.29, 6.90, 7.30, 7.88, 8.00, 8.73, 9.54, 9.67, 10.01, 10.18, 10.99, 11.25, 11.50, 11.87, 12.28, and 12.67 ppm; $\delta_{TMS}^{CCl_4-CDCl_3}$ 5.55 (vinylic H) and 3.60 ppm (CH_2OH).

7a-Benzyloxymethyl-2,4,5,6,7,7a-hexahydroindene-3-carboxaldehyde (30).—A solution of 3.33 g (20.1 mmol) of alcohol **28** in 170 ml of dioxane was added to heptane-washed NaH (from 1.93 g of 57% oil dispersion) and the mixture was stirred at reflux for 2 hr. The cooled solution was treated with 3.48 ml (5.00 g, 29.2 mmol) of benzyl bromide and refluxing was continued for 16 hr whereupon the product was isolated with ether and distilled, affording 5.83 g of ether **29** contaminated with benzyl bromide, bp 140° (bath temperature) at 0.01 mm: λ_{max}^{film} 3.30, 6.71, 6.91, 7.39, 8.35, 9.15, 9.78, 11.02, 11.52, 13.68, and 14.41 μm; $\delta_{TMS}^{CCl_4}$ 7.20 (aromatic H's), 5.35 (vinylic H), 4.40

(27) A 6 ft × 0.12 in. column of 10% UCON W-98 on 80–100 mesh Diatoport-S was used.

(benzylic H's), and 3.40 ppm (carbinyl CH_2, AB, $J = 9$, $\Delta\nu = 12$ Hz). The analytical sample was obtained by two successive short-path distillations.

Anal. Calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found: C, 84.4; H, 9.6.

A 240-mg sample of the above olefin in 16 ml of methylene chloride at −78° was treated with a stream of ozonized oxygen until the solution became blue. The excess ozone was allowed to evaporate and 1.6 ml of acetic acid followed by 0.8 g of zinc powder were added with stirring at −78°. The mixture was allowed to reach room temperature, stirred for 10 min, and filtered. The product was isolated with ether, affording 242 mg of crude keto aldehyde: λ_{max}^{film} 3.30, 3.69, 5.80, 5.86, 6.71, 6.91, 7.35, 7.91, 8.38, 9.11, 9.76, 13.62, and 14.38 μm; $\delta_{TMS}^{CCl_4}$ 9.58 (CHO triplet, $J = 2$ Hz), 7.20 (aromatic H's), 4.42 (benzylic H's), and 3.47 ppm (carbinyl CH_2, AB, $J = 9$, $\Delta\nu = 11$ Hz).

The above material was stirred at 60° with 240 mg of sodium carbonate and 2 ml of water in 40 ml of ethanol for 22 hr. The product was isolated with ether–benzene and chromatographed on silica gel to give 120 mg (54%) of unsaturated aldehyde **30**: λ_{max}^{film} 3.28, 3.65, 5.98, 6.10, 6.68, 6.88, 7.38, 7.89, 8.28, 9.12, 9.72, 11.81, 13.60, and 14.35 μm; $\delta_{TMS}^{CCl_4}$ 9.88 (aldehyde CH), 7.20 aromatic H's), 4.43 (benzylic H's), and 3.37 ppm (carbinyl CH_2).

3,7a-Bishydroxymethyl-5,6,7,7a-tetrahydroindan (32).—To a solution of triphenylmethyllithium[28] (from 1.54 g of triphenylmethane and 3.8 ml of 1.5 *M* methyllithium) in 1,2-dimethoxyethane (7 ml) was added 0.400 g of aldehyde **30**, comparable to that described above, in 7 ml of 1,2-dimethoxyethane dropwise with stirring over a 0.5-hr period. After 1 hr the solution was added to a well-stirred solution containing 20 g of sodium borohydride and 20 ml of water in 152 ml of ethanol. The solution was stirred for 3.5 hr and poured into 10% aqueous NaOH, and the product was isolated with ether–benzene. The triphenylmethane was removed by precipitation from cold pentane and filtration through a column of silica gel, affording 233 mg of alcohol **31** contaminated with the isomeric allylic alcohol: λ_{max}^{film} 2.92, 3.31, 6.70, 6.91, 7.38, 8.32, 9.15, 9.33, 9.72, 11.26, 13.62, and 14.35 μm; $\delta_{TMS}^{CCl_4}$ 7.15 (aromatic H's), 5.40 (vinylic H), 4.35 (benzylic H's), 3.4–3.2 (C-3 carbinyl CH_2), and 3.11 ppm (C-7a carbinyl CH_2). The analytical sample was prepared by preparative layer chromatography (silica) followed by short-path distillation (120° at 0.03 mm).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.7; H, 9.1.

To a stirred solution of 0.37 g of Li wire in 70 ml of ammonia at −78° was added 0.23 g of alcohol **31**, comparable to that described above, in 3 ml of tetrahydrofuran and 2 ml of *tert*-butyl alcohol. After 1 hr at −78° and 2 hr at −33° (reflux) ethanol was slowly added to discharge the blue color and the ammonia was allowed to evaporate. The product was isolated with ethyl acetate, purified by preparative layer chromatography (silica), and distilled to give 0.11 g (41% based on aldehyde **30**) of diol **32**, bp 160° (bath temperature) at 0.10 mm: λ_{max}^{film} 3.00, 5.98, 6.88, 8.00, 8.65, 9.75, 10.45, and 11.33 μm; $\delta_{TMS}^{CCl_4\text{-}CDCl_3}$ 5.53 (vinylic H) and 3.8–3.3 ppm (–CH_2OH multiplet).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.4; H, 10.2.

3-Methyl-7a-hydroxymethyl-5,6,7,7a-tetrahydroindan (33).—To a stirred solution of 82 mg (0.30 mmol) of alcohol **31**, comparable to that described above, in 0.7 ml of pyridine at 0° was added 0.135 ml (1.78 mmol) of methanesulfonyl chloride. After 0.5 hr at 0° and 2 hr at room temperature, the mixture was cooled to 0° and was added slowly to a solution containing 2 ml of water in 5 ml of pyridine at 0°. The product was isolated with ether, affording 79 mg of mesylate: λ_{max}^{film} 3.28, 6.90, 7.40, 8.52, 9.15, 9.75, 10.30, 10.63, 11.24, 12.00, 13.45, and 14.36 μm; $\delta_{TMS}^{CCl_4}$ 7.20 (aromatic H's), 5.55 (vinylic H), 4.42 (benzylic H's), 4.02 and 3.92 (CH_2OMs, two doublets, $J = 1$–2 Hz), 3.17 (C-7a carbinyl CH_2), and 2.75 ppm (CH_3SO_3).

The above mesylate in 0.67 ml of ethanol and 0.35 ml of tetrahydrofuran was added dropwise to a stirred solution of 0.124 g of lithium in 10 ml of ammonia at −78°. After 1.5 hr at −78° and 1 hr at −33° (reflux) ammonium chloride was added, the ammonia was allowed to evaporate through a mercury bubbler, and the product was isolated with ether and distilled, affording 35 mg of alcohol **33**, bp 95° (bath temperature) at 0.04 mm (87% pure according to gas chromatography[22]): λ_{max}^{film} 2.96, 3.29, 6.89, 7.31, 8.00, 9.76, 10.33, 10.43, 10.71, 11.04, 11.35, 11.61, and 12.95 μm; $\delta_{TMS}^{CCl_4}$ 5.50 (vinylic H), 3.40 (carbinyl CH_2), and 1.04 ppm (CH_3 doublet, $J = 7$ Hz). The anaytical sample, mp 27–33°, was prepared by preparative layer chromatography (silica) and two successive short-path distillations.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.6; H, 10.9.

Cyclization of Diol 32 to Ether 34.—A stirred solution of 0.103 g of diol **32** in 2 ml of pyridine at −40° was treated dropwise with 47 μl (71 mg) of methanesulfonyl chloride. After 4 hr at −10° and 6 hr at room temperature the mixture was cooled to 0° and ice chips were slowly added. The product was isolated with ether, affording 0.128 g of crude hydroxy mesylate: λ_{max}^{film} 2.94, 3.31, 6.87, 7.45, 8.53, 9.72, 10.27, 10.65, and 11.95 μm; $\delta_{TMS}^{CCl_4\text{-}CDCl_3}$ 5.68 (vinylic H) and 3.00 ppm (CH_3SO_3).

The above material in 35 ml of dioxane was treated with pentane-washed NaH (from 0.35 g of 57% mineral oil dispersion) and the mixture was stirred at room temperature for 2 hr, at 70° for 1 hr, and at reflux for 3 hr. The cooled mixture was poured onto ice and the product was isolated with pentane and distilled, affording 35 mg of ether **34**, bp 90° (bath temperature) at 20 mm: λ_{max}^{film} 6.90, 7.84, 8.28, 8.73, 9.03, 9.28, 10.02, 10.16, 10.28, 10.43, 11.14, 11.82, 12.07, and 12.48 μm; $\delta_{TMS}^{CCl_4}$ 5.35 (vinylic H, unresolved triplet) and 3.6–3.3 ppm (–CH_2O– multiplet). The analytical sample was obtained by preparative layer chromatography (silica) and short-path distillation.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.2; H, 10.0.

3-Acetylbicyclo[5.3.0]dec-1(7)-en-3-ol (36).—The method of Corey was employed.[17] A solution of 1.8 g of 1,3-dithiane in 60 ml of tetrahydrofuran was cooled to −30° and 5.4 ml of 2.8 *M* butyllithium was added with stirring. After 1.5 hr, the solution was allowed to reach −5° and 2.26 g of methyl iodide was added dropwise. The mixture was kept at −5° for 20 hr and a 20-ml aliquot was removed, cooled to −30°, and treated with 2 ml of 2.8 *M* butyllithium with stirring. After 2.25 hr, a solution of 0.59 g of ketone **10** in 5 ml of tetrahydrofuran was added. After 36 hr at −5° the reaction mixture was concentrated under reduced pressure and the product was isolated with ether, affording 1.15 g of crude alcohol **35** whose infrared spectrum showed unreacted ketone **10**. Accordingly the mixture was subjected to the above procedure (54 hr at −5°) whereupon 1.3 g of alcohol **35** was obtained nearly free of ketone **10** but contaminated with 2-methyl-1,3-dithiane: λ_{max}^{film} 2.88, 5.88 (trace), 6.95, 7.08, 7.32, 7.89, 8.10, 8.42, 9.49, 9.93, and 11.02 μm; $\delta_{TMS}^{CCl_4}$ 3.0–2.6 (–SCH_2– multiplet) and 1.60 ppm (CH_3).

The above thioketal alcohol in 56 ml of acetonitrile and 2.9 ml of water containing 3.3 g of mercuric chloride and 1.96 g of cadmium carbonate was stirred at 55° for 11 hr.[17] An additional 0.3 g of mercuric chloride and 0.2 g of cadmium carbonate were then added (an aliquot showed the presence of starting material) and heating was continued for 3 hr. The mixture was filtered and the product was isolated with ether and distilled, affording 0.49 g of keto alcohol **36**, bp 120° (bath temperature) at 0.05 mm: λ_{max}^{film} 2.90, 5.86, 6.97, 7.44, 8.50, 9.10, and 9.85 μm; $\delta_{TMS}^{CCl_4}$ 2.35 (allylic H's) and 2.16 ppm (CH_3CO). The analytical sample was prepared by preparative layer chromatography (silica) and short-path distillation.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.0; H, 9.4.

3-Acetylbicyclo[5.3.0]dec-1(7)-en-3-yl Acetate (37).—The procedure of Saucy was employed.[29] A 0.19-g sample of the crude keto alcohol **36** was stirred with 0.59 ml of acetic anhydride and 5.5 μl of phosphoric acid for 0.5 hr. The product was isolated with ether and partially purified by preparative layer chromatography (silica) and distillation, affording 0.11 g of material, bp 120° (bath temperature) at 0.2 mm, which contained 80% of acetoxy ketone **37** and 18% of ketone **10** according to the gas chromatogram:[27] λ_{max}^{film} 5.74, 5.81, 6.97, 7.32, 7.42, 8.01, 8.11, 8.41, 9.26, and 9.83 μm. The analytical sample was prepared from comparable material by preparative layer chromatography (silica) and two successive short-path distillations.

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.2; H, 8.5.

3-Acetylbicyclo[5.3.0]dec-1(7)-ene (38).—To a stirred solution of 1.48 g of Ca turnings in 150 ml of ammonia at −78° was added 110 mg of 80% pure (see above) acetoxy ketone **37** dissolved in 6 ml of tetrahydrofuran. After 10 min sufficient bromo-

(28) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341 (1965).

(29) G. Saucy, *Helv. Chim. Acta*, **42**, 1945 (1959).

benzene was added dropwise to discharge the blue color and excess ammonium chloride was added. The ammonia was allowed to evaporate and the product was isolated with ether and purified by short-path distillation, preparative layer chromatography (silica), and short-path distillation (100° at 0.15 mm) to give 49 mg (74%) of ketone **38**: λ_{max}^{film} 5.83, 6.94, 7.42, 8.18, 8.33, and 9.61 μm; $\delta_{TMS}^{CCl_4-CDCl_3}$ 2.05 ppm (CH_3CO).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.8; H, 10.2.

2-(3-Bicyclo[5.3.0]dec-1(7)-enyl)-2-propanol (39).—To a stirred solution containing 34 mg of ketone **38** in 3 ml of ether at 0° was added 1.0 ml of 1.5 *M* methyllithium. After 3.5 hr at room temperature, the mixture was poured onto ice and the product was isolated with ether. The material thus secured still contained 15% of ketone **38**.[27] The above procedure was thus repeated and the product distilled, affording 35 mg (94%) of alcohol **39**, bp 85° (bath temperature) at 0.2 mm, shown to be 85% pure by gas chromatography:[27] λ_{max}^{film} 2.97, 6.95, 7.32, 7.67, 8.87, 10.50, 11.02, 11.32, and 11.61 μm; $\delta_{TMS}^{CCl_4}$ 1.10 ppm (CH_3). The analytical sample secured by preparative layer chromatography (silica) and distillation exhibited mp 54–55.5° after sublimation at 25° (0.04 mm).

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.4; H, 11.4.

Registry No.—**2** methyl ester, 29494-06-2; **2** ethyl ester, 29494-34-6; **3** methyl ester, 29494-07-3; **3** ethyl ester, 29494-35-7; **4**, 29494-08-4; **5**, 29494-09-5; **6**, 29494-10-8; **7**, 29494-11-9; **8**, 29494-12-0; **9**, 7125-60-2; **10**, 29494-14-2; **11**, 29494-15-3; **13** methyl ester, 29494-16-4; **13** ethyl ester, 29494-36-8; **14** methyl ester, 29494-17-5; **14** ethyl ester, 29576-49-6; **15** methyl ester, 29494-18-6; **15** ethyl ester, 29494-37-9; **16**, 29494-19-7; **17**, 29478-14-6; **18**, 29478-15-7; **19**, 29478-16-8; **20**, 29478-17-9; **21**, 29478-18-0; **22**, 29478-19-1; **23**, 29494-20-0; **26** methyl ester, 29494-21-1; **26** ethyl ester, 7478-39-9; **27** methyl ester, 29494-22-2; **27** ethyl ester, 2088-98-4; desulfurized **27** methyl ester, 29494-24-4; desulfurized **27** ethyl ester, 29494-25-5; **29**, 29494-26-6; **30**, 29494-27-7; **31**, 29478-20-4; **31** mesylate, 29576-48-5; **32**, 29478-21-5; **32** monomesylate, 29472-24-0; **33**, 29478-22-6; **34**, 29494-28-8; **35**, 29494-29-9; **36**, 29494-30-2; **37**, 29494-31-3; **38**, 29494-32-4; **39**, 29494-33-5.

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The Acid-Catalyzed Alkylation and Cyclialkylation of the Cymenes with Isobutylene and Related Olefins[1a]

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The acid-catalyzed reactions of *o*-, *m*-, and *p*-cymene with isobutylene, diisobutylene, and triisobutylene give complex mixtures of hydrocarbon products. *o*-Cymene forms only alkylation products, whereas *p*-cymene gives predominantly cyclialkylation products, with only one case of alkylation. *m*-Cymene occupies an intermediate position, providing both alkylation and cyclialkylation products. The reactions of *m*- and *p*-cymene with these olefins afford indans and tetralins as cyclialkylation products. In the cyclialkylation products from *m*-cymene, the point of ring closure (ortho or para position to the methyl group) is strongly influenced by an alkyl group at the 5 position of *m*-cymene. Several acidic materials were used to catalyze the reactions of *p*-cymene with isobutylene, diisobutylene, and triisobutylene, and their effectiveness is compared. Some new hydrocarbons were isolated and identified. These are obtained from alkylation and cyclialkylation of the starting olefin or result from olefins produced in the reaction system *via* polymerization, rearrangement, and fragmentation.

Cyclialkylation reactions initiated by hydride ion abstraction were discovered by Pines and coworkers.[2a] They found that aromatic hydrocarbons having α tertiary hydrogens may undergo hydride ion abstraction by carbonium ions generated in the reaction medium. Their mechanism[2a] is shown in Scheme I using isobutylene as the olefin to give 1,1,3,3,5-pentamethylindan (**2**), first identified by Schlatter.[2b] As pointed out by Barclay,[2c] alkylation competes with cyclialkylation. Alkylation will predominate unless the aromatic hydrocarbons used are substituted so as to sterically hinder alkylation reactions. In addition, branched olefins (or compounds such as branched-chain alcohols which can generate such olefins in acidic media) seem necessary since straight-chain alcohols have been reported[2c,d] to react with *p*-cymene to give only alkylation products.

A variety of substituted indans, hydrindacenes, and tetralins have been prepared[2c] with *p*-cymene, whereas Barclay[2e] used 1,3,5-triisopropylbenzene and diisobutylene to prepare a neopentylindan. Most of the work has been with *p*-cymene, *m*- and *o*-cymene[2c,f] having been used in only a few cases, and no previous studies have dealt extensively with minor products.

(1) (a) D. E. Boone, E. J. Eisenbraun, P. W. Flanagan, and R. D. Grigsby, *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, **15**, 77 (1970). (b) American Petroleum Institute Graduate Research Assistant, 1967–1969.

(2) (a) V. N. Ipatieff, H. Pines, and R. C. Olberg, *J. Amer. Chem. Soc.*, **70**, 2123 (1948); (b) M. J. Schlatter, "Symposium on Petrochemicals in the Postwar Years," 124th National Meeting of the American Chemical Society, Chicago, Ill., 1953, p 79; (c) L. R. C. Barclay, "Friedel–Crafts and Related Reactions," Vol. 2, part 2, G. A. Olah, Ed., Interscience, New York, N. Y., 1964, p 785; (d) S. H. Weber, J. Stofberg, D. B. Spoelstra, and R. J. C. Kleipool, *Recl. Trav. Chim. Pays-Bas*, **75**, 1433 (1956); (e) L. R. C. Barclay, J. W. Hilchie, A. H. Gray, and N. D. Hall, *Can. J. Chem.*, **38**, 94 (1960); (f) H. Pines, D. R. Strehlau, and V. N. Ipatieff, *J. Amer. Chem. Soc.*, **72**, 5521 (1950); (g) Queries regarding samples of hydrocarbons **2**, **8**, and **10** should be directed to A. J. Streiff, American Petroleum Institute, Carnegie-Mellon University, Pittsburgh, Pa. 15213.

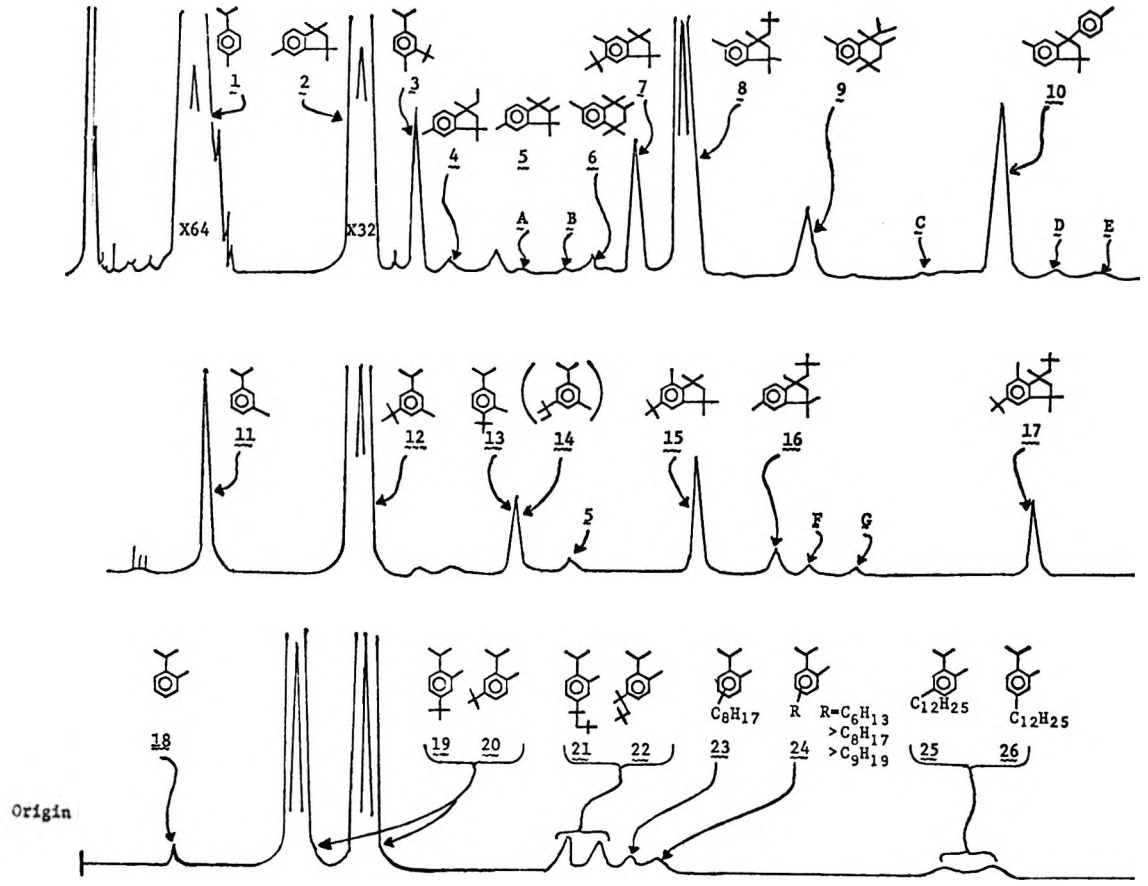
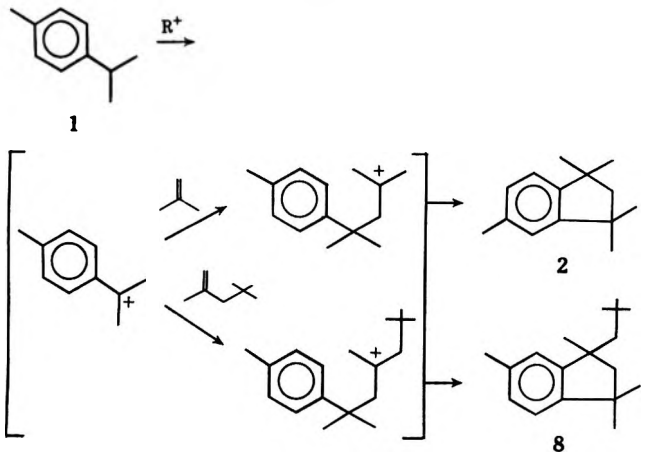


Figure 1.—Gas chromatograms of *o*-, *m*-, and *p*-cymene–isobutylene reaction products.

SCHEME I



The cyclialkylation reaction has been a valuable source of hydrocarbons for us.[2g] In the current work, *p*-cymene (**1**) and isobutylene, as well as diisobutylene, provided 1,1,3,3,5-pentamethylindan (**2**)[2b] and 1,3,3,6-tetramethyl-1-neopentylindan (**8**) in quantity[2g] as shown in Scheme I. The variety of products found in these reactions and not previously reported prompted us to reexamine the *p*-cymene–isobutylene reaction and to extend the study to other olefins and other cymenes. The cymenes were selected for study since they include the necessary variation in alkyl substitution which permits both extremes of alkylation and cyclialkylation. As previously mentioned, in the absence of steric effects (three or more vicinal hydrogens present), alkylation is the predominant reaction. Actually, as shown in Figure 1 for the alkylation of *o*-cymene, there were no products due to cyclialkylation. The requirement for cyclialkylation includes a tertiary benzylic hydrogen and an unsubstituted adjacent position on an aromatic ring. With *p*-cymene, eight components were identified as cyclialkylation products but only one, **3**, a minor product, is due to alkylation. As expected, *m*-cymene occupies an intermediate position in regard to these reactions and both effects may be symmarized as follows: for alkylation, *o*- > *m*- ≫ *p*-cymene, and for cyclialkylation, *o*- ≪ *m*- < *p*-cymene.

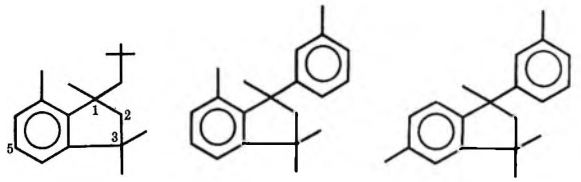
The formation of all hydrocarbons identified in this study may be rationalized through application of existing carbonium ion theories.[3,4] The formation of all the products shown accompanying the top and middle glc curves of Figure 1 except **4**, **5**, **6**, and **14** may be explained by using the mechanism of Scheme I and/or an added alkylation step.[2a–f,3] These four anomalous hydrocarbons cannot be formed directly from isobutylene or diisobutylene and require an olefin fragmentation and/or rearrangement[3a,4] to 2-methyl-1-butene and 2-methyl-2-butene as well as 2,3-dimethyl-1-butene to explain their formation. It should be noted that hydrocarbons **4**, **5**, **6**, and **14** and those unidentified ones having empirical formulas which could not arise from isobutylene or its condensation products also could not arise from impurities in the starting materials since glc

(3) (a) L. Schmerling, ref 2c, p 1075; (b) H. Pines and N. E. Hoffman ref 2c, p 1211.

(4) (a) A. Schneider, *J. Amer. Chem. Soc.*, **174**, 2553 (1952); (b) J. E. Hofmann, *J. Org. Chem.*, **29**, 3627 (1964); (c) G. J. Karabatsos, F. M. Vane, and S. Meyerson, *J. Amer. Chem. Soc.*, **85**, 733 (1963).

analyses ruled out significant amounts of impurities.[5a] In addition, *p*-cymene and diisobutylene were carefully purified by preparative glc[5b] and these purified samples were subjected to sulfuric acid catalyzed condensation. No significant differences in the products from this and conventional runs were observed. While structure **9** represents a C_{18} hydrocarbon, its formation cannot be rationalized from diisobutylene except through skeletal rearrangement to 2,3,4-trimethylpentenes and subsequent reaction with *p*-cymene to form the tetralin **9** rather than an indan in a reaction analogous to that described by Wood.[6]

For the most part, the products of the isobutylene and diisobutylene reactions are comparable, although there there is some variation in ratios. A notable exception is that diisobutylene and *m*-cymene provide 1,3,3,7-tetramethyl-1-neopentylindan (**27**), which appears to be absent in the reaction products when isobutylene is used. The glc retention time of **27** is the same as that of F in Figure 1; however, **27** and F are not the same. The formation of **27** is of interest because it could be expected to predominate over **16** by



27 **28** **29**

analogy with the fact that in a similar reaction 1,3,3,7-tetramethyl-1-*m*-tolylindan (**28**) and 1,3,3,5-tetramethyl-1-*m*-tolylindan (**29**) were found in a 2:1 ratio.[7a] However, when α,*m*-dimethylstyrene is treated with diisobutylene, the ratio of **16**:(**17** + **27**) is 1.4. Since the neopentyl group is bulkier than the *m*-tolyl group, a steric effect may cause the formation of more **16** relative to **17** + **27**. The formation of **17** from **27** is to be expected since position 5 of **27** is unhindered for tertiary butylation. Thus the absence of **27** in the *m*-cymene–isobutylene reaction products is not surprising. The 5 position is also unhindered for other reactions, such as sulfonation, which could influence the combined yield of **17** and **27**. It is of interest that *m*-cymene is readily alkylated by isobutylene to give **12**, which corresponds to reaction at C-5. It would also be expected that diisobutylene should react with *m*-cymene in an analogous manner to form the homolog with an octyl (C_8H_{17}) group at this same position. Our glc and mass spectral data failed to give evidence for its formation and hence initial alkylation is not prerequisite to cyclialkylation when diisobutylene is used.

Cyclialkylation is the more important reaction for *p*-cymene. *m*-Cymene may undergo alkylation[2c,f] to **12** followed by cyclialkylation to **15** and **17**. Formation of **15** and **17** may also be explained by cyclialkylation of *m*-cymene with ring closure ortho to the methyl group followed by alkylation at position 5 as discussed above for **27**.

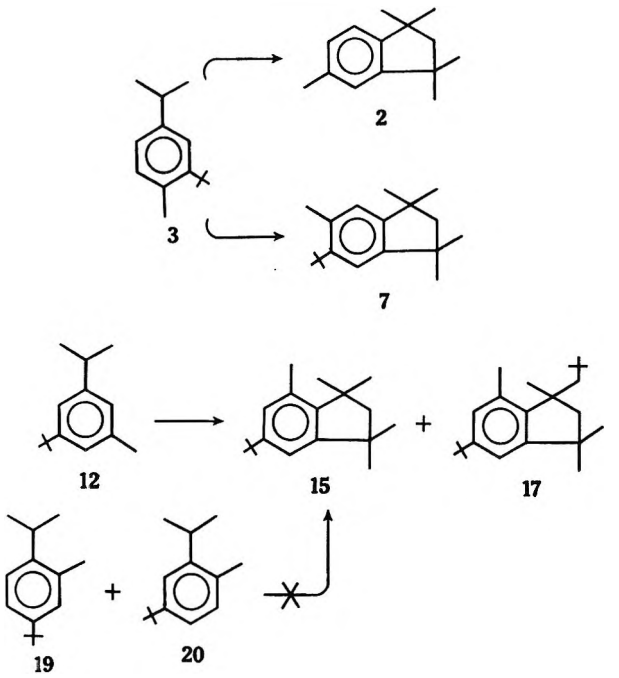
(5) (a) We thank Mr. E. Smith, Analytical Research Section, Continental Oil Co., Ponca City, for helpful assistance with these capillary glc studies. (b) We thank R. E. Laramy, Analytical Research Section, Continental Oil Co., for these separations.

(6) T. F. Wood, W. M. Easter, Jr., M. S. Carpenter, and J. T. Angiolini, *J. Org. Chem.*, **28**, 2248 (1963).

(7) (a) J. C. Petropoulos and J. J. Fisher, *J. Amer. Chem. Soc.*, **80**, 1938 (1958); (b) M. J. Schlatter, U. S. Patent 2,768,982 (1956).

Scheme II shows the products of several experiments devised to probe alkylation *vs.* cyclialkylation. It is

SCHEME II



of interest that **3** with isobutylene not only underwent cyclialkylation to form **7** but also suffered de tertiary butylation to form the conventional cyclialkylation product **2**. The sterically and thermodynamically more stable **12** underwent cyclialkylation with no observable dealkylation to give **15** and **17** on treatment with isobutylene and H_2SO_4. Significantly, no reaction was observed for a mixture of **19** and **20** on treatment with isobutylene and H_2SO_4. It would be expected that **20** would not undergo cyclialkylation because of the steric influence of the *tert*-butyl group. However, it might be expected that **19** could undergo cyclialkylation with isobutylene to form **15**. The lack of reactivity of **19** becomes apparent upon examination of a molecular model which shows the tertiary hydrogen of **19** to be less available for abstraction than the tertiary hydrogens of *m*- or *p*-cymene since the approach of a cation to this site is effectively blocked by the surrounding methyl groups. This argument applies to *o*-cymene and explains the absence of cyclialkylation products.

Several minor or trace products from the cymene–olefin reactions were isolated by preparative glc and analyzed by mass and nmr spectroscopy. However, some of these were contaminated by polymeric hydrocarbons that obscured interpretation of the spectra and consequently their structures remain unknown at this time. These hydrocarbon samples are designated by letters; the available data are presented in Figure 1 as well as in the Experimental Section.

The products obtained are the same whether isobutylene, diisobutylene, triisobutylene, or tetraisobutylene is combined with *p*-cymene. However, the olefin used does affect the product ratios, which are shown in Table I.

When sulfuric acid was used, the best results were obtained with a reaction temperature below 10° (runs 1a, 1b, 5a–c). As the temperature was increased (runs

TABLE I

ACID-CATALYZED REACTIONS OF THE CYMENES AND OLEFINS

Run[b]	°C	Moles			2[c]	Glc ratios of major hydrocarbons[a]				
		Acid	Cymene	Olefin		5	8	8	9	10
1a[d]	5[e]	1.14[f]	12.9[g]	6[h]	41			0.15	0.03	0.09
1b	5[e]	0.19[f]	0.25[g]	3[h]	42			0.09	0.01	0.10
2a	10[e]	0.07[i]	0.50[g]	9[h]	2			0.32	0.53	
2b	115	0.26[i]	0.34[g]	6.4[h]	43	0.03		0.04	0.02	0.02
3a	25[e]	7[j]	0.50[g]	24[h]	1			2.00	0.71	
3b	85	5.5[j]	0.25[g]	48[h]	15			0.10	0.03	
3c	130	3.5[j]	0.25[g]	39[h]	33			0.06	0.07	0.05
4	5[e]	1.4[k]	1.07[g]	2[h]	12	0.02		0.32	0.03	0.03
5a	5	0.19[f]	0.25[g]	0.50[l]	9	0.24	0.06	5.04	0.61	0.52
5b	5	0.76[f]	0.25[g]	0.50[l]	7	0.18	0.08	7.53	1.05	1.46
5c[d]	5	0.74[f]	8.20[g]	13.2[l]	7	0.19	0.05	7.40	0.74	0.13
5d	25	0.11[f]	0.25[g]	0.50[l]	8			2.40	0.41	0.14
5e	25	0.19[f]	0.25[g]	0.50[l]	17	0.07	0.06	2.76	0.53	0.43
5f	25	0.39[f]	0.25[g]	0.50[l]	10	0.08	0.0	2.22	0.50	0.42
5g	65	0.10[f]	0.50[g]	1.0[l]	2			1.40	0.47	
6a[m]	70	0.19[f]	0.25[g]	0.50[l]	25	0.12	0.07	0.39	0.19	
6b	70	0.10[f]	0.09[g]	0.19[l]	27	0.15	0.07	0.31	0.16	0.03
6c	115	0.25[f]	0.33[g]	0.67[l]	43	0.05		0.08	0.05	0.09
6d	140	0.19[f]	0.25[g]	0.50[l]	35	0.12	0.05	0.19		
7	100	69[j]	0.29[g]	0.88[l]	12			1.20	0.54	0.11
8a	5	1.0[k]	0.25[g]	0.54[l]	15	0.12	0.0	2.05	0.18	0.04
8b	5	2.5[k]	0.25[g]	0.54[l]	23	0.15	0.06	1.19	0.16	
9a	5	0.12[n]	0.25[g]	0.25[l]	Trace	0.04		50[o]		
9b[m]	70	0.12[n]	0.50[g]	0.50[l]	13			2.7	0.17	
10	5	0.10[f]	0.20[g]	0.14[p]	18	0.11	0.108	0.74	0.06	0.13
11	5	0.07[n]	0.20[g]	0.18[p]	5	0.48		10.2		1.06
12	5	0.10[f]	0.50[g]	0.20[q]	1.0[r]	4.6				0.3
13a[m]	5	0.03[f]	1.00[g]	0.10[s]	1.0[r]	0.5				
13b	5	0.10[f]	0.50[g]	0.25[s]	1.0[r]	0.5		6.4	12.5	3.5
13c	5	0.03[f]	0.06[g]	0.13[s]	1.0[r]	0.6		1.3	2.0	0.2

					8	12	13 + 14	15	16	17
14	10[e]	0.07[f]	0.50[u]	4[h]	0.01	1.00	0.09	0.21	0.07	0.12
15	5	0.02[f]	0.07[u]	0.22[l]	0.0	1.00	0.97	0.25	2.53	1.14

					19 + 20	21 + 22	23	24	25 + 26
16	10[e]	0.07[f]	0.50[w]	6.0[h]	1.0	0.02	0.002	0.001	0.01
17	5	0.06[f]	0.15[w]	0.30[l]	1.0	1.06	0.21	0.00	0.00
18	5	0.06[f]	0.15[w]	0.16[p]	1.0	0.23	0.11	0.03	0.08

[a] Product normalized to 2 = 1.00. [b] Magnetic stirring except where noted. [c] Values given are per cent yield of 2 based on *p*-cymene except as noted. [d] Vibromixer E-2. [e] °C controlled by flow of isobutylene. [f] H_2SO_4. [g] *p*-Cymene. [h] Hours isobutylene flow. [i] Methanesulfonic acid. [j] Amberlyst-15 in grams. [k] HF. [l] Diisobutylene. [m] Motor-driven turbine stirrer. [n] $AlCl_3$. [o] Peak ratios are compared to 8 = 1.00; the value for 8 is per cent yield. [p] Triisobutylene. [q] 2-Methyl-2-butene. [r] Ratio only, not a per cent yield. [s] 2,3,4-Trimethyl-2-pentene. [t] Glc ratio of major hydrocarbons normalized to 12 = 1.00. [u] *m*-Cymene. [v] Glc ratio of hydrocarbons normalized to 19 + 20 = 1.00. [w] *o*-Cymene.

5a–f), the yield of low-molecular-weight polyisobutylenes increased until, at 65° (run 5g), only a few per cent of the products resulted from cyclialkylation reactions, and the major product observed on glc was tetraisobutylene.

Within limits, the quantity of sulfuric acid used had little effect on the products formed. When a low molar concentration of sulfuric acid (acid to *p*-cymene ratio of 1:10, run 1a) was used, more tetraisobutylene and other olefinic polymers resulted. Large amounts of sulfuric acid, *i.e.*, acid to *p*-cymene ratio of 2:1 or greater, resulted in loss of material due to sulfonation and consequent emulsion formation during isolation (run 5b).

Anhydrous hydrogen fluoride (runs 4, 8a, and 8b) was effective in catalyzing the cyclialkylation reaction.[7b] In run 4, the isobutylene introduced into the reaction did not approach the stoichiometric amount; therefore, the 12% yield of 2 formed is not a true indication of this acid's ability to catalyze the reaction. With hydrogen fluoride, the diisobutylene reaction (runs 8a and 8b) gave much less of the cyclialkylation product 8 than with sulfuric acid (runs 5a and 5b) and more fragmentation of diisobutylene occurred. An increased concentration of hydrogen fluoride produced larger yields of fragmentation products.

Methanesulfonic acid (run 2a) gave only olefin polymerization at temperatures below 30°. This catalyst at 70° (runs 6a and 6b) still caused formation of reaction products that were badly contaminated by polymeric material, but it did then yield cyclialkylation products. When the reaction temperature was 115° and above (runs 2b, 6c, and 6d), the amount of polymeric material decreased. The yields of 2 increased while little 8 was formed, indicating that considerable fragmentation of diisobutylene was occurring.

When Amberlyst-15 was the catalyst, it was necessary to use temperatures in excess of 100° (runs 3a–c)

TABLE II

INSTRUMENTAL DATA FOR HYDROCARBONS DERIVED FROM *o*-, *m*-, AND *p*-CYMENE

2[a] Bp 42° (0.5 mm) [lit.[k] 153.6° (100 mm)]; ir 815 and 878 cm^{-1}; nmr δ 1.24 (s, 12, $-CH_3$ β to aromatic ring), 1.86 (s, 2, CH_2), 2.27 (s, 3, Ar CH_3), 6.81–6.87 (m, 3, Ar H). *Anal.* Calcd for $C_{14}H_{20}$: C, 89.29; H, 10.71. Found: C, 89.27; H, 10.56.

3[a] Ir 812 (s) and 881 cm^{-1} (m); nmr δ 1.15 and 1.25 [d, $CH(CH_3)_2$], 1.38 [s, 9, $C(CH_3)_3$], 2.43 (s, 3, Ar CH_3), 2.73 (m, 1, CH), 6.80–7.11 (m, 3, Ar H); mass spectrum M = 190, 175 (M − 15) loss of methyl group, 147 (M − 43) loss of C_3, 133 (M − 57) loss of C_4; see lit.[2b] for preparation.

4[b] Ir 815 (s) and 878 cm^{-1} (m); nmr δ 0.80 (t), 1.02 (s), 1.22 (s), 1.25 (s), 1.58 (m), 1.81 (m), 2.29 (s, 3, Ar CH_3), 6.74–6.86 (m, 3, Ar H); mass spectrum M = 202, 187 (M − 15) and 173 (M − 29) loss of methyl and ethyl groups; see lit.[l] for preparation.

5[b] Ir 815 (s) and 879 cm^{-1} (m); nmr δ 0.91 (this is half of a doublet $CHCH_3$ and corresponds to 1.5 protons; the other half is hidden by the 1.04 peak), 1.04 (s, 7.5, geminate dimethyl protons, hides half of the previously listed doublet), 1.26 (s, 6, geminate dimethyl protons), 1.75 (q, 1, CH), 2.30 (s, 3, Ar CH_3), 6.83–6.89 (m, 3, Ar H); mass spectrum M = 202, 187 (M − 15) loss of methyl group; see lit.[l] for preparation.

6[c] Mp 64–66° (lit.[6] mp 66–67.5°); mass spectrum M = 216, 201 (M − 15) loss of methyl group. Ir, mass, and nmr spectra all agree with those of the known compound.[m]

7[a] Mp 81–82°; ir (CS_2) 880 (s, appears as a shoulder on the next peak) and 887 cm^{-1} (s); mass spectrum M = 244, 229 (M − 15) loss of methyl group;[n] nmr δ 1.26 (s, 12, geminate CH_3), 1.40 [s, 9, $C(CH_3)_3$], 1.86 (s, 2, CH_2), 2.49 (s, 3, Ar CH_3), 6.70 (s, 1, Ar H), and 6.96 (s, 1, Ar H). *Anal.* Calcd for $C_{18}H_{28}$: C, 88.45; H, 11.55. Found: C, 88.57; H, 11.63.

8[d] Bp 84–85° (0.5 mm); ir 815 (s) and 878 cm^{-1} (m); mass spectrum M = 244, 173 (M − 71) loss of C_5 group; nmr δ 1.03 [s, 9, $C(CH_3)_3$], 1.24, 1.28, 1.32 (three s, 3 protons each, CH_3 β to benzene ring), 1.65 (center of AB quartet, 2, CH_2), 2.03 (center of AB quartet, 2, CH_2), 2.27 (s, 3, Ar CH_3), and 6.81–6.87 (m, 3, Ar H). *Anal.* Calcd for $C_{18}H_{28}$: C, 88.45; H, 11.55. Found: C, 88.63; H, 11.39.

9[e] Bp 87–88° (0.5 mm); ir 758 (w), 816 (s), 887 (m), and 895 (w) appears as a shoulder on the 887 cm^{-1} peak; mass spectrum M = 244, 201 (M − 43) loss of C_3 group(s); nmr δ 0.71, 0.82, 0.91, 1.01 (the four preceding peaks account for 18 protons), 1.44 and 1.54 (2 protons), 2.03 (m, 2 protons), 2.22 (s, 3, Ar CH_3), 6.73–7.16 (m, 3, Ar H). *Anal.* Calcd for $C_{18}H_{28}$: C, 88.45; H, 11.55. Found: C, 88.24; H, 11.56.

10[a] Mp 40–41° (lit.[7a] 37–38°, 40°); ir agrees with published[2a] spectrum; nmr δ 1.03, 1.30, 1.62 (three s, 3 protons each, CH_3 β to the aromatic ring), 2.21 (center of partially hidden AB quartet, 2, CH_2), 2.21, 2.28 (two s, 3 protons each, Ar CH_3), and 6.71–7.10 (m, 7, Ar H).[o]

12[f] Ir 711 (s), 815 (w), 857 (s), and 882 cm^{-1} (w); mass spectrum M = 190, 175 (M − 15) loss of methyl group (mass spectral analysis shows a second component with M = 188); intensity ratio of 190 to 188 is 10:1; nmr δ 1.17 [3 H, one-half of doublet from $CH(CH_3)_2$], 1.28 [s, 12, $C(CH_3)_3$, also covers the other half of isopropyl doublet], 2.29 (s, 3, Ar CH_3), 2.81 (m, 1, Ar H), 6.72 (s, 1, Ar H), and 6.88 (s, 2, Ar H). Comparisons of glc retention times and ir and mass spectra indicate that the minor component is **2**.

13[f] Ir 712 (m), 823 (s), 857 (m), and 880 cm^{-1} (m); mass spectrum, mixture, M = 190 and 204 (intensity ratio *ca.* 5:1), 175 (M − 15 or M − 29) loss of methyl or ethyl group; nmr δ 1.14 (s), 1.25 (m), 2.37 (s), 2.28 (two s, Ar CH_3) in a 1:2 ratio), and 6.70–7.20 (m, Ar H). Comparisons of ir and mass spectra indicate that the major component is **13** and the minor component is **14**.

14[g] Ir 711 (s) and 858 cm^{-1} (s); mass spectrum M = 204, 175 (M − 29) loss of ethyl group (s); nmr δ (no integration values are given since the sample was contaminated with polymeric material) 1.17, 1.23, 1.27 (CCH_3), 1.40–1.80 (m, CH_2), 2.38 (s, Ar CH_3), 2.45–2.90 (m, Ar CH), 6.70–6.89 (m, Ar H).

15[f] Ir 655 (m), 770 (m), and 872 cm^{-1} (s); mass spectrum M = 244, 229 (M − 15) loss of methyl group; nmr δ 1.26 (s, 6, unhindered geminate dimethyl group), 1.28 [s, 9, $C(CH_3)_3$], 1.37 (s, 6, hindered geminate dimethyl group), 1.86 (s, 2, CH_2), 2.34 (s, 3, Ar CH_3), and 6.82 (s, 2, Ar H).

16[h] Ir 815 (s) and 878 cm^{-1} (m); mass spectrum M = 244, 173 (M − 71) loss of C_5 group; nmr δ (this sample was contaminated with polymeric material, thus the integration values are not included) 1.00 [s, $C(CH_3)_3$], 1.25 and 1.28 (two s, the latter being stronger and having a shoulder), 2.37–2.33 (m, two overlapping AB quartets from two nonequivalent CH_2 groups), 2.28 (s, Ar CH_3), and 6.75–6.88 (m, Ar H).

17[h] Ir 653 (m), 774 (w), and 870 cm^{-1} (s); mass spectrum M = 300, 229 (M − 71) loss of C_5 group; nmr δ 1.03 [s, 9, $C(CH_3)_3$], 1.24 (s, 3, a geminate methyl group), 1.28 [s, 12, Ar $C(CH_3)_3$ and a geminate methyl group], 1.46 (s, 3, methyl group geminate to the neopentyl group), 1.50–2.50 (m, 4, two nonequivalent CH_2 appearing as two overlapping AB quartets), 2.37 (s, 3, Ar CH_3), and 6.75–6.90 (m, 2, Ar H).

19[i] or 20[i] Ir 645 (w), 733 (m), 816 (s), 862 (w), and 888 cm^{-1} (m); nmr δ 1.16 [3, half of doublet resulting from the isopropyl methyls, $CH(CH_3)_2$; the other half is covered by the next peak mentioned], 1.29 [s, 12, $C(CH_3)_3$ and three protons from $CH(CH_3)_2$], 2.25 (s, 3, Ar CH_3), 3.08 (m, 1, Ar CH), 6.94 (m, 2, Ar H), 7.14 (m, 1, Ar H).

19[i] or 20[i] Ir 825 (s) and 881 cm^{-1} (m); nmr δ 1.14 [3, half of the doublet from $CH(CH_3)_2$], 1.27 [s, 12, $C(CH_3)_3$ and three protons from $CH(CH_3)_2$], 2.29 (s, 3, Ar CH_3), 3.07 (m, 1, Ar CH), 7.03 (m, 3, Ar H).

21 Mass spectrum M = 246, 175 (M − 71) loss of C_5 group.

22 Mass spectrum M = 246, 175 (M − 71) loss of C_5 group.

23 Mass spectrum M = 246, 175 (M − 71) loss of C_5 group.

24 Mass spectrum (mixture) M = 218, 246, 260; intensity ratio *ca.* 3.3:2.2:1.0.

25 Mass spectrum M = 302, 175 (M − 127) loss of C_9 group.

26 Mass spectrum M = 302, 175 (M − 127) loss of C_9 group.

TABLE II
(*Continued*)

27[i]	Ir 729 (m), 746 (s), and 788 cm^{-1} (s); nmr δ 1.01 [s, 9, $C(CH_3)_3$], 1.21 (s, 3, geminate CH_3), 1.30 (s, 3, geminate CH_3), 1.47 (s, 3, CH_3 geminate to the neopentyl group), 1.50–2.50 (m, 4, two overlapping AB pattern groups), 2.39 (s, 3, Ar CH_3), 6.65–7.0 (m, 3, Ar H); mass spectrum M = 244.2192 (calcd for $C_{18}H_{28}$, 244.2191), 229 (M − 15) loss of methyl group, 187 (M − 57) loss of C_4, 173 (M − 71) loss of C_5.
A[a]	Ir spectrum was identical with that of a known sample of 1-isopropyl-1,3,3,6-tetramethylindan;[m] mass spectrum M = 216, 173 (M − 43) loss of C_3 group, in agreement with this structure.
B[a]	Ir 814 (s) and 878 cm^{-1} (m); mass spectrum M = 230, 173 (M − 57) loss of C_4 group (s); nmr δ 0.75–1.25 (m), 1.30 (s, 9, CH_3 β to benzene ring), 1.34–2.25 (m), 2.29 (s, 3, Ar CH_3), 6.75–6.95 (m, 3, Ar H) (integration values are given only when the contaminants did not interfere). This hydrocarbon is thought to be 1-*sec*-butyl-1,3,3,6-tetramethylindan.
C	Mass spectrum = 258, 173 (M − 85) loss of C_6 group(s).
D	Mass spectrum M = 300, 229 (M − 71) loss of C_5 group(s).
E	Mass spectrum M = 300, 201 (M − 99) loss of C_7 group(s).
F[e]	Ir 655 (w), 765 (s), 790 (m), 815 (w), and 870 cm^{-1} (s); mass spectrum M = 258, 229 (M − 29) and 173 (M − 85) loss of ethyl and C_6 groups, respectively.
G[e]	Ir 653 (m), 769 (m), and 870 cm^{-1} (s); mass spectrum M = 258, 243 (M − 15) and 229 (M − 29) loss of methyl and ethyl groups.

Preferred starting materials for synthesis of the above hydrocarbons: [a] *p*-cymene and isobutylene; [b] *p*-cymene and 2-methyl-2-butene; [c] *p*-cymene and 2,3-dimethyl-1-butene; [d] *p*-cymene and diisobutylene; [e] *p*-cymene and 2,3,4-trimethyl-1-pentene; [f] *m*-cymene and isobutylene; [g] *m*-cymene and 2-methyl-2-butene; [h] *m*-cymene and diisobutylene; [i] *o*-cymene and isobutylene; [j] α,*m*-dimethylstyrene and diisobutylene. [k] M. J. Schlatter, *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, 1, no. 2, 77 (1956). [l] D. B. Spoelstra, S. H. Weber, and R. J. C. Kleipool, *Recl. Trav. Chim. Pays-Bas*, 82, 1100 (1963). [m] We thank Mr. T. F. Wood, Givaudan Corp., for kindly supplying references samples of 6 and 1-isopropyl-1,3,3,6-tetramethylindan. [n] We thank M. C. Hamming, Analytical Research Section, Continental Oil Co., for the mass spectrum of 7. [o] We thank Dr. R. J. Lee and Amoco Chemicals Corp. for a generous sample of *m*-cymene and hydrocarbon 10.

to minimize the polyisobutylene formation. Comparison of run 6a with run 7 shows that while the yield of **2** is doubled in comparing methanesulfonic acid to Amberlyst-15, the ratio **8**:**2** is increased in the latter reaction. This shows that even at a higher temperature, Amberlyst-15 gives more intact cyclialkylation products than methanesulfonic acid.

Aluminum chloride (run 9a) at 5° gave essentially no products resulting from cleavage of diisobutylene. A trace of **2** and a large yield of **8** was obtained. When the reaction temperature was increased to 70° (run 9b), indan **2** was formed, but **8** was still the major product. With triisobutylene and aluminum chloride (run 11), a large amount of **8**, but no significant amounts of higher molecular-weight cyclialkylation products, was observed.

The ir bands in the regions 815 and 880 cm^{-1} corresponding to 1,2,4 trisubstitution on a benzene ring were observed.[8] There were no significant deviations due to structure, *e.g.*, **2** (a 5-methylindan), **3** (a trialkylbenzene), and **9** (a 6-methyltetralin) gave the appropriate bands. In addition, correlations with model hydrocarbons were made as follows: **7** at 880 and 887 cm^{-1} with 1,2,4,5-tetramethylbenzene (CS_2); **12** at 711 and 857 cm^{-1} and **14** at 712 and 857 cm^{-1} with 1,3,5-trimethylbenzene (neat liquids); **15** at 655, 770, and 872 cm^{-1} and **17** at 653, 774, and 870 cm^{-1} with an authentic sample of 6-*tert*-butyl-4-ethyl-1,1-dimethylindan (1,2,3,5 tetrasubstitution) at 647, 768, and 872 cm^{-1}; and **27** at 729, 764, and 788 cm^{-1} with 1,2,3-trimethylbenzene (see Table II).

Experimental Section[9]

Samples for instrumental analyses were obtained by preparative gas–liquid chromatography (glc) with an F & M Model 700 gas chromatograph equipped with dual thermal conductivity detectors. A 13 ft × 0.25 in. column containing 5% silicone rubber UCW-98 on 80–100 mesh, dimethyldichlorosilane- (DMCS) treated, acid-washed Chromosorb G was used with helium as carrier gas.

Hydrocarbons **2** and **8** were purified by preparative glc using an F & M Model 776 gas chromatograph fitted with hydrogen flame detectors. An 8 ft × 4 in. column containing Carbowax 20M on 80–100 mesh, acid-washed Gas Pac was used with nitrogen as carrier gas.

Qualitative glc analyses were obtained with an F & M Model 5754B apparatus fitted with dual thermal conductivity and hydrogen flame detectors using helium as carrier gas. A 12 ft × $^1/_8$ in. column containing 10% silicone rubber UCW-98 on 80–100 mesh, DMCS-treated, acid-washed Chromosorb W was used. These data were generally obtained by temperature programming from 130 to 300° at 4°/min.

The sulfuric acid used was 97%. The Amberlyst-15 was a gift from the Rohm and Haas Co.

Acid-Catalyzed Reactions of *p*-Cymene and Isobutylene. Run 1b.—A 250-ml three-necked Morton flask was equipped with a gas inlet tube, a magnetic bar, and a thermometer and cooled in an ice bath. In the flask were placed 33.5 g (0.25 mol) of *p*-cymene and 19.0 g of H_2SO_4. After cooling the reaction vessel to 5°, isobutylene was bubbled into the stirred and cooled reaction mixture for 3 hr at a rate which kept the temperature 10°. The H_2SO_4 layer was separated and the organic layer was poured over solid Na_2CO_3, filtered, washed with saturated Na_2CO_3 solution, and dried ($MgSO_4$) to give 71.4 g of reaction products.

Hydrogen Fluoride Catalyzed Reaction of *p*-Cymene with Isobutylene. Run 4.—The polyethylene equipment consisted of a 500-ml wide-mouth bottle fitted with a three-holed lid having a sintered gas dispersion tube, a gas exit tube, and a stainless steel sheathed thermocouple. In the bottle were placed 144 g (1.07 mol) of *p*-cymene, and after cooling to 5°, 28 g (1.4 mol) of anhydrous HF were introduced. Isobutylene was bubbled into the magnetically stirred reaction mixture for 2 hr at a rate which kept the reaction temperature below 10°.

The reaction mixture was poured over ice, and a solution of 40% NaOH was added. The organic layer was separated and dried ($CaCl_2$) yielding 165 g of reaction products. The aqueous layer was extracted twice with ether, and after drying ($CaCl_2$),

(8) R. T. Conley, "Infrared Spectroscopy," Allyn & Bacon, Boston, Mass., 1966.

(9) Mass spectra were obtained with a Consolidated Electrodynamics Model 21-110B high-resolution mass spectrometer which was operated under low-resolution conditions using electron energy of 70 eV. Nmr spectra were obtained with a Varian HR-60 and A-60 spectrometers. Peak positions are reported as δ parts per million (ppm) downfield from internal tetramethylsilane standard in carbon tetrachloride solvent. Ir spectra were obtained with a Beckman IR-5A spectrometer as films on sodium chloride plates unless otherwise stated. Melting points were measured in degrees centigrade, taken in capillary melting point tubes using a Thomas-Hoover apparatus and are corrected.

the extract was concentrated to yield 10 g more of organic material.

The other reactions catalyzed with HF were run in the same apparatus, with the olefin being added from a polyethylene dropping funnel instead of the gas inlet tube.

Acid-Catalyzed Reactions of *p*-Cymene with Diisobutylene. Run 5a.—This run was like run 1b except that the olefin (56 g, 0.50 mol) was added from a pressure-equalizing funnel over a 1-hr period. The yield of products was 77.6 g. The above description, modified as given in Table I, is typical of all the reactions using di-, tri-, and tetraisobutylene.

Preparation of 1,3,3,6-Tetramethyl-1-neopentylindan (8) from *p*-Cymene and Diisobutylene. Run 5c.—In a 5-l. Morton flask equipped with a 2-l. dropping funnel and a thermocouple were placed 1100 g (8.2 mol) of *p*-cymene. This was cooled to 5° and sulfuric acid, 72 g, was introduced. Diisobutylene, 1480 g (13.2 mol), was added dropwise to the reaction mixture, which was stirred with a large Vibromixer. The temperature was kept below 10° throughout the 2.5 hr required to add the olefin and during the additional 3 hr the mixture was stirred. The mixture was worked up as in run 1b. Glc analysis showed a 43% yield of **8**.

A distillation fraction [bp 82–88° (0.5 mm)] from run 5c in which **8** was concentrated was subjected to preparative glc at 150° using the apparatus previously described. The material collected was distilled and then passed through a column of silica gel and acidic and basic alumina to give 92 g of **8** (see Table II).

Registry No.—**1**, 99-87-6; **2**, 81-03-8; **3**, 29577-13-7; **4**, 29641-87-0; **5**, 4834-28-0; **7**, 29577-15-9; **8**, 29577-16-0; **9**, 29577-17-1; **10**, 1153-36-2; **12**, 29577-19-3; **13**, 29577-20-6; **14**, 29577-21-7; **15**, 29577-22-8; **16**, 29641-88-1; **17**, 29577-23-9; **19**, 29577-24-0; **20**, 29577-25-1; isobutylene, 115-11-7; *o*-cymene, 527-84-4; *m*-cymene, 535-77-3.

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Acid-Catalyzed Reactions of Propiolophenone and 2-Ethynyl-2-phenyl-1,3-dioxolane with Ethylene Glycol[1]

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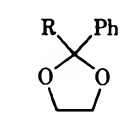
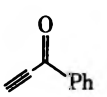
An attempt to prepare 2-ethynyl-2-phenyl-1,3-dioxolane (**1a**) from propiolophenone (**2**), *p*-toluenesulfonic acid, and excess ethylene glycol resulted instead in the formation of 2-phenyl-2,2′-methylenebis-1,3-dioxolane (**3**) and/or 2-methyl-2-phenyl-1,3-dioxolane (**1b**). With a small amount of *p*-toluenesulfonic acid the former product predominated, but with equimolar propiolophenone and acid only the latter was formed. It was found that **3** could be converted to **1b** with equimolar *p*-toluenesulfonic acid. A synthesis of **1a** from 2-(1-bromoethyl)-2-phenyl-1,3-dioxolane (**5**) is described. Compound **1a** was found to be stable to the conditions which converted **2** to **3**. This observation and certain spectroscopic evidence indicate that **3** is formed from **2** *via* 1-oxo-1-phenyl-3-(1,3-dioxolane)propane (**4**).

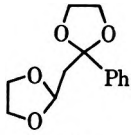
An attempt to prepare 2-ethynyl-2-phenyl-1,3-dioxolane (**1a**) from propiolophenone (**2**), a small amount of anhydrous *p*-toluenesulfonic acid, and excess ethylene glycol in refluxing benzene with constant removal of benzene–water azeotrope yielded instead 2-phenyl-2,2′-methylenebis-1,3-dioxolane (**3**) (84%). The acetylenic proton of **1a** was not observed in the nmr spectrum of the crude product from this reaction, but this spectrum did exhibit a singlet with a chemical shift identical with that of the methyl group of 2-methyl-2-phenyl-1,3-dioxolane (**1b**). Integration revealed that the **3**:**1b** ratio was 13:1. When an equivalent amount of **2** and anhydrous *p*-toluenesulfonic acid and excess ethylene glycol were similarly reacted, **1b** was the only product that could be isolated (52%). The nmr spectrum of the crude product from this reaction revealed the absence of **1a** and **3**. Finally, when an equivalent amount of **3** and anhydrous *p*-toluenesulfonic acid and excess ethylene glycol were similarly reacted, **1b** again was the only product that could be isolated (35%).



1a, R = –C≡CH
b, R = –CH_3



2

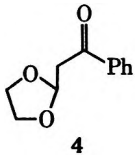


3

When equivalent amounts of **2** and ethylene glycol and a catalytic quantity of anhydrous *p*-toluenesulfonic acid were refluxed in benzene, the product was a multicomponent oil. Its nmr spectrum contained a large multiplet, the chemical shift of which was roughly the same as that previously found for the OCH_2CH_2O systems of **3** and **1b**. This spectrum also contained the characteristic doublet (τ 7.79) and triplet (τ 5.18) of **3**, a second doublet (τ 6.76) and triplet (τ 4.67), and a signal in the aromatic region. Two components, one an oil and the other a solid, resulted when this mixture was subjected to plc. Nmr analysis revealed the solid to be **2**. It was not detected in the nmr of the original oil since its acetylenic proton falls in the same region as the dioxolane ring protons. The new oil exhibited a carbonyl absorption at 5.84 μ. Further attempts to separate it by plc resulted in small amounts of pure **3**, but the carbonyl-containing substituent could not be isolated. The nmr of this oil again exhibited a pair of doublets and a pair of triplets, and aromatic plus dioxolane ring protons. The areas under the signals due to the aromatic and dioxolane ring protons were greater than would be predicted were they to have arisen from **3** alone, but what one would predict if the second component possessed one phenyl group and one dioxolane ring. We feel the spectroscopic evidence strongly implies that the third component was 1-oxo-1-phenyl-3-

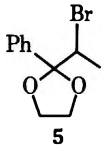
(1) Presented in part at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., April 1971.

(1,3-dioxolane)propane (**4**). The three yields follow: **2** (30%), **3** (34%), and **4** (14%).



4

The sequence of steps finally employed for the synthesis of **1a** is virtually identical with that used by Feugeas and Giusti for their synthesis of 2-ethynyl-2-methyl-1,3-dioxolane from 2-(1-bromoethyl)-2-methyl-1,3-dioxolane.[2] The only facet of our work worthy of mention is the preparation of 2-(1-bromoethyl)-2-phenyl-1,3-dioxolane (**5**). The analogous compound in the



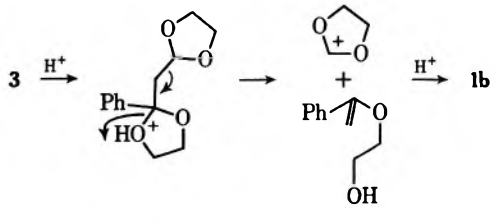
5

French workers' series was prepared *via* ketalization of the appropriate α-bromo ketone, but in our case the requisite α-bromo ketone cannot be easily obtained.[3] However, we have found that Eaton's conditions[4] produce a good yield of **5** from 2-ethyl-2-phenyl-1,3-dioxolane.

When **1a** was subjected to the conditions which converted **2** to **3** nmr analysis of the crude product revealed that no reaction had occurred.[5] This fact and the observation that **1a** is not seen during the conversion **2** → **3** show that if **1a** is ever formed during this conversion it is present in minute quantities, and if present it obviously does not react directly with *p*-toluenesulfonic acid–ethylene glycol to form **3**. Consideration of these data and the fact that an intermediate with spectral properties strongly suggestive of **4** is observed during the conversion **2** → **3** causes us to assume that **4** is the prime intermediate in this conversion.

The facile formation of **3** from **2** and the fact that **3** yields **1b** when treated with anhydrous *p*-toluenesulfonic acid suggest the conversion **2** → **1b** proceeds at least in part *via* fragmentation of **3** (Scheme I). This fragmentation is similar to one discovered by Kraus (Scheme II).[6]

SCHEME I



Our inability to isolate pure **4** has so far precluded experiments which would ascertain whether or not any product is formed *via* its fragmentation.

(2) C. Feugeas and G. Giusti, *C. R. Acad. Sci., Ser. C*, **264**, 1772 (1967).

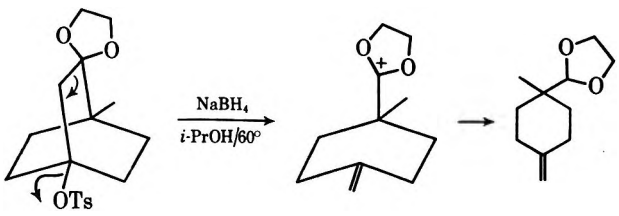
(3) F. Kröhnke and H. Timmler, *Chem. Ber.*, **69**, 614 (1936).

(4) P. E. Eaton, *J. Amer. Chem. Soc.*, **84**, 2344 (1962). We acknowledge a fruitful discussion with Professor R. E. Lehr.

(5) The conditions must be strictly anhydrous since **1a** is readily hydrolyzed to **2** in the presence of even trace quantities of hydronium ion.

(6) W. Kraus and C. Chassin, *Justus Liebigs Ann. Chem.*, **735**, 198 (1970).

SCHEME II



Experimental Section

Melting points were obtained on an Arthur H. Thomas Co. Unimelt apparatus and are uncorrected. Microanalyses were carried out by Chemalytics, Inc., Tempe, Ariz. Infrared spectra were obtained using a Beckman IR-8 recording spectrophotometer. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60 spectrometer. In all cases carbon tetrachloride was employed as solvent and tetramethylsilane (τ 0.00 ppm) as internal reference. Mass spectra (80 eV) were obtained by Professor R. E. Lehr, Mr. J. M. Wilson, and Mr. R. W. Allen using a Hitachi Perkin-Elmer Model RMU-7 double-focusing mass spectrometer equipped with a direct inlet system. Analytical scale thin layer chromatography (tlc) and preparative layer chromatography (plc) plates were prepared using silica gel PF-254 366 (E. Merck AG).

Unless otherwise noted the following standard work-up procedure was employed. The crude reaction mixture was poured into 100 ml of ether and extracted with three 30-ml portions of 10% potassium hydroxide and one 30-ml portion of saturated sodium chloride. After drying the organic phase with anhydrous magnesium sulfate, the solvent was removed at reduced pressure with the aid of a rotary evaporator and steam bath.

Propiolophenone (**2**).—The method of Bowden, Heilbron, Jones, and Weedon[7] was used to prepare propiolophenone, mp 49–50° (lit.[7] mp 50–51°).

2-Methyl-2-phenyl-1,3-dioxolane (**1b**) **and 2-Ethyl-2-phenyl-1,3-dioxolane.**—The method of Salmi, Tamminen, and Louhenkuru[8] was used to prepare authentic samples of 2-methyl-2-phenyl-1,3-dioxolane, mp 58–59° (lit.[8] mp 60–61°), and 2-ethyl-2-phenyl-1,3-dioxolane, bp 65° (1.8 mm) [lit.[8] bp 87.7° (3 mm)].

2-(1-Bromoethyl)-2-phenyl-1,3-dioxolane (**5**).—A solution of 2-ethyl-2-phenyl-1,3-dioxolane (19.0 g, 0.11 mol) in 70 ml of tetrahydrofuran was cooled to 0° and 35.2 g (0.11 mol) of pyridinium bromide perbromide was added in one portion.[4] The resulting mixture was stirred at 0° for 3 hr and 25° for 4 hr and filtered into a separatory funnel. The standard work-up procedure was used but the potassium hydroxide extractions were preceded by one with 40 ml of dilute sodium thiosulfate. Short-path distillation of the resulting oil afforded a forerun, bp 58–66° (0.2 mm), which was discarded and a main fraction, bp 79–89° (0.2 mm), which weighed 23.0 g (84%). It was sufficiently pure for use in the next step of the sequence. The analytical sample was a center cut from a second distillation (12-mm Vigreux column): bp 112° (0.7 mm); ir (neat) 9.27, 9.76, 14.18 μ; nmr τ 2.36–2.85 (m, 5 H), 5.48–5.85 (q, partially superimposed on the OCH_2CH_2O multiplet), 5.72–6.40 (m), 8.44 (d, 3 H, J = 6.9 Hz). The mass spectrum of this material showed a parent doublet at m/e 256 and 258 and a base peak at m/e 149.

Anal. Calcd for $C_{11}H_{13}O_2Br$: C, 51.37; H, 5.11. Found: C, 51.52; H, 5.06.

2-Ethenyl-2-phenyl-1,3-dioxolane.—Potassium *tert*-butoxide (12.0 g, 0.11 mol, Alfa Inorganics-Ventron, Beverly, Mass.) was added to dimethyl sulfoxide (100 ml), and after the solution was cooled to 0° 20.9 g (0.08 mol) of 2-(1-bromoethyl)-2-phenyl-1,3-dioxolane was added over a 1.5-hr period. The mixture was stirred for 1.5 hr at 0° and 20 hr at 25°. Standard work-up procedure gave an oil, short-path distillation of which produced a liquid: bp 59–68° (0.3 mm); 13.5 g (95%); ir (neat) 9.39, 9.84, 14.29 μ; nmr τ 2.42–2.92 (m, 5 H), 3.79–5.05 (m, 3 H), 5.92–6.42 (m, 4 H). The mass spectrum of this material showed a parent ion at m/e 176 and a base peak at m/e 149.

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.96; H, 6.87. Found: C, 75.12; H, 6.78.

(7) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(8) E. J. Salmi, U. Tamminen, and P. Louhenkuru, *Suom. Kemistilehti, B*, **20**, 1 (1947).

2-(1,2-Dibromoethyl)-2-phenyl-1,3-dioxolane.—2-Ethenyl-2-phenyl-1,3-dioxolane (17.2 g, 0.098 mol) was dissolved in 100 ml of carbon tetrachloride and cooled to 0°. Bromine was added dropwise until the color was no longer discharged. The standard work-up procedure was used but the potassium hydroxide extractions were preceded by one with 50 ml of dilute sodium thiosulfate. A slightly yellow solid resulted, mp 80–83°. Four crystallizations from methanol provided the analytical sample: white microprisms; mp 81.5–83°; ir (KBr) 8.23, 9.50, 10.03, 10.48, 14.22 μ; nmr τ 2.37–2.82 (m, 5 H), 5.50–6.82 (m, 7 H). The mass spectrum of this materal did not exhibit a parent ion. The base peak was at m/e 149 and there was a low intensity triplet at m/e 257, 259, 261.

Anal. Calcd for $C_{11}H_{12}O_2Br_2$: C, 39.31; H, 3.60. Found: C, 39.17; H, 3.58.

2-Ethynyl-2-phenyl-1,3-dioxolane (1a).—A suspension of sodamide in 150 ml of liquid ammonia was prepared from 10.6 g (0.46 g-atom) of sodium.[9] To this stirred solution 27.2 g (0.081 mol) of 2-(1,2-dibromoethyl)-2-phenyl-1,3-dioxolane was added over 30 min (no solvent). After an additional 1.5 hr 21 g of ammonium chloride was added followed by 400 ml of ether. The yellow oil which remained after the standard work-up procedure was distilled, bp 92–96° (0.6 mm), giving 11.3 g (80%) of a colorless liquid. Silica gel plc (29% ether–hexane) gave the analytical sample: ir (neat) 3.03, 4.73, 9.32, 9.74 μ; nmr τ 2.19–2.87 (m, 5 H), 5.70–6.24 (m, 4 H), 8.39 (s, 1 H). The mass spectrum of this material showed a parent ion at m/e 174 and base peak at m/e 97.

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.90; H, 5.90.

2-Methyl-2-phenyl-1,3-dioxolane (1b) from Propiolophenone (2).—*p*-Toluenesulfonic acid monohydrate (2.25 g, 12 mmol), 4 ml of ethylene glycol, and 50 ml of benzene were refluxed for 1 hr with azeotropic removal of water. This solution was cooled to room temperature and 1.44 g (11 mmol) of propiolophenone was added in one portion. Reflux was resumed for 16.5 hr after which the solution was worked up in the standard fashion. Sublimation [50–60° (2 mm)] of the resulting oil afforded 0.95 g (52%) of a white crystalline solid, mp 58–61° (lit.[6] mp 60–61°). The infrared and nmr spectra obtained were identical with those of an authentic sample of 2-methyl-2-phenyl-1,3-dioxolane.

2-Phenyl-2,2′-methylenebis-1,3-dioxolane (3).—*p*-Toluenesulfonic acid monohydrate (0.025 g, 0.13 mmol), 4 ml of ethylene glycol, and 20 ml of benzene were refluxed for 10 min with azeotropic removal of water. The solution was cooled to room temperature and 0.63 g (4.8 mmol) of propiolophenone was added. The new mixture was refluxed for 4 hr with azeotropic removal of water and cooled to room temperature. Standard work-up gave 1.06 g of oil which appeared (nmr) to be a mixture of **2** and **1b** (13:1). Trituration with ether–hexane gave 0.95 g (84%) of a white prismatic solid which melted at 53–54.5° after three crystallizations from ether–hexane: ir (KBr) 9.62, 13.99 μ; nmr τ 2.46–2.93 (m, 5 H), 5.08–5.28 (t, 1 H, J = 7.8 Hz), 5.89–6.47 (m, 8 H), 7.72–7.85 (d, 2 H, J = 7.8 Hz). The mass spectrum of this material did not exhibit a parent ion. The base peak appeared at m/e 149. There were also sizable ions at m/e 73 and 105. The mass spectrum of a similar molecule is in the literature.[10]

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.17; H, 6.78.

Reaction of Propiolophenone (2) with 1 Equiv of Ethylene Glycol.—A mixture of 0.697 g (11 mmol) of ethylene glycol, 0.032 g (0.17 mmol) of *p*-toluenesulfonic acid monohydrate, and 20 ml of benzene was refluxed with azeotropic removal of water for 15 min. The mixture was cooled to room temperature and 1.47 g (11 mmol) of propiolophenone was added. This mixture was refluxed for 3 hr with azeotropic removal of water and cooled to room temperature. Standard work-up procedure gave 2.00 g of oil; nmr analysis indicated the presence of 2-phenyl-2,2′-methylenebis-1,3-dioxolane (**3**) and a second compound which exhibited a triplet (τ 4.56–4.78, J = 8.1 Hz) and doublet (τ 6.69–6.83, J = 8.1 Hz). Two bands resulted from plc (successive developments with 15, 28, and 52% ether–hexane). The material isolated from the band with the greatest R_f proved to be **2** (0.43 g, 30%). The material isolated from the second band was an oil (1.12 g) which exhibited the characteristic nmr peaks of **3** and the unknown doublet and triplet. Also, nmr integration revealed the phenyl and OCH_2CH_2O regions contained more protons than would result from **3** alone. The ir of this oil showed a carbonyl absorption at 5.84 μ. The spectral data strongly suggest that the third component of the mixture was 1-oxo-1-phenyl-3-(1,3-dioxolane)propane (**4**); based on this assumption the yields of the three compounds were as follows: **2** (30%), **3** (34%), and **4** (14%).

Attempted Reaction of 2-Ethynyl-2-phenyl-1,3-dioxolane (1a) with Ethylene Glycol.—*p*-Toluenesulfonic acid monohydrate (0.07 g, 0.37 mmol), ethylene glycol (0.07 g, 1.2 mmol), and 30 ml of benzene were refluxed with azeotropic removal of water for 15 min. This solution was cooled to room temperature and 0.10 g (0.59 mmol) of propiolophenone was added. The new mixture was refluxed for 4.3 hr with azeotropic removal of water and with a calcium chloride drying tube affixed to the condenser and then cooled to room temperature. Standard work-up procedure left 0.10 g of an oil. Nmr analysis showed this to be mainly **1a**; the characteristic peaks of **1b**, **3**, and **4** were missing.

Reaction of 2-Phenyl-2,2′-methylenebis-1,3-dioxolane (3) with Equimolar *p*-Toluenesulfonic Acid.—*p*-Toluenesulfonic acid monohydrate (0.40 g, 2.1 mmol), 1.2 ml of ethylene glycol, and 20 ml of benzene were refluxed with azeotropic removal of water for 10 min. This solution was cooled to room temperature and 0.58 g (2.4 mmol) of 2-phenyl-2,2′-methylene bis-1,3-dioxolane was added. The new mixture was refluxed for 47 hr and cooled to room temperature. Standard work-up procedure gave 0.68 g of oil; sublimation [50–60° (2 mm)] afforded 0.14 g (35%) of a white crystalline solid, mp 58–61° (lit.[8] mp 60–61°). The infrared and nmr spectra were identical with those of an authentic sample of 2-methyl-2-phenyl-1,3-dioxolane.

Registry No.—**1a**, 29568-62-5; **2**, 3623-15-2; **3**, 29568-64-7; **5**, 29568-65-8; ethylene glycol, 107-21-1; 2-ethenyl-2-phenyl-1,3-dioxolane, 29568-66-9; 2-(1,2-dibromoethyl)-2-phenyl-1,3-dioxolane, 29568-67-0.

(9) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 1034.

(10) G. A. Russell and L. A. Ochrymowycz, *J. Org. Chem.*, **34**, 3618 (1969).

Conformational Analysis. LXXIII. The Perhydroanthracenes. An Equilibration Study[1,2]

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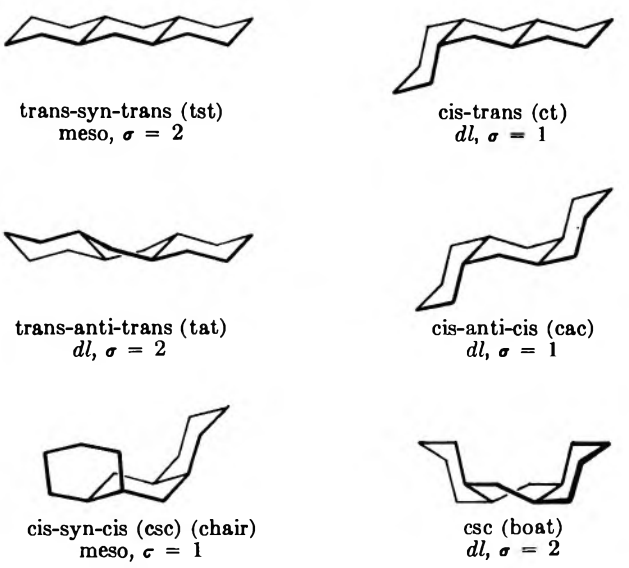
The heats of formation of the isomeric perhydroanthracenes (gas phase, 25°) have been calculated by a force-field method described previously to be −57.68, trans-syn-trans; −55.06, cis-trans; −51.82, trans-anti-trans; −52.04, cis-anti-cis; −49.74 kcal/mol, cis-syn-cis. These relative values are consistent with equilibration experiments.

There are five stereoisomers possible for perhydroanthracene, all of which have previously been described in the literature.[3] Because this basic ring system is simple and of wide occurrence in nature, the relative stabilities of the possible stereoisomers are of interest. The conformational analysis of these compounds was carried out at an early date,[4] and the pertinent conformations are shown. The heats of formation (*via* heats of combustion) (gas phase) have been reported for two of the isomers.[5] We now have available a force field which has been developed[6] for studying similar molecules, and it seemed advantageous to reexamine the conformational calculations with the aid of molecular mechanics. In addition, it was deemed desirable to actually bring the isomers to equilibrium and determine the percentage composition of the mixture. Further, by determining the composition as a function of temperature, it is possible to obtain the enthalpies and entropies for the isomerization for each of the equilibria under consideration. The methods and procedures follow generally along the lines discussed previously for the perhydrophenanthrenes[7] and related compounds.[8]

Previous equilibration studies of the perhydroanthracenes have been carried out.[3c,d] They employed aluminum bromide as catalyst, which usually leads to skeletal rearrangements as well as epimerizations. The results showed that the free energy difference between the two most stable isomers was similar to that predicted by Johnson. The other isomers were not detected at the low temperatures (0–25°) used.

Experimental Section

Perhydroanthracene (a mixture containing 69.7% csc, 26.5% ct, 2.9% cac, and 0.9% tst) was obtained by hydrogenation of anthracene in ethanol with the aid of reduced platinum oxide catalyst and a trace of hydrochloric acid. The reaction was carried out at 2–3-atm pressure at 85°, two replacements of the catalyst being necessary to bring the reaction to completion. Equilibrations were then carried out on the neat material at 200–350° in sealed glass tubes in the presence of 10% Pd/C catalyst. The equilibrated solid was dissolved in hexane and analyzed by vpc. The individual isomers were identified by comparison with known samples, three of which were provided by Dr. R. L. Clarke (tat, tst, and cac). The remaining two samples (csc and ct) were isolated from the hydrogenation mixture by preparative vpc. They were identified by comparing their physical properties with those described in the literature.



Synthetic mixtures of isomers were prepared and used to calibrate the vpc analyses. The product ratios were determined in each case in duplicate by planimetry of the vpc traces. Small amounts of side products, probably from dehydrogenation, were noted, but none of these interfered significantly with the analyses. These side products did not appear to change in amount with time after the main products had reached equilibrium, and thus they were at equilibrium too. The possibility that we are looking at steady states rather than equilibria can therefore be discounted.

To be certain that equilibrium had been reached at a given temperature, samples equilibrated for increasing lengths of time were analyzed, and the isomer ratios eventually became constant. At least three vpc traces were obtained for all samples near equilibrium.

Results

The percentage of each isomer in the equilibrium mixture at each temperature was recorded as an average of several determinations, and these numbers are summarized in Table I. The relative percentages of the two major isomers can be easily determined, but the other three isomers are present in rather small amounts, and the error in their determination is considerable.

(1) Paper LXXII: N. L. Allinger, C. L. Neumann, and H. Sugiyama, *J. Org. Chem.*, **36**, 1360 (1971).

(2) Supported in part by Grant No. AM-5836 from the National Institute of Arthritis and Metabolic Diseases.

(3) (a) R. L. Clarke, *J. Amer. Chem. Soc.*, **83**, 965 (1961); (b) J. W. Cook, N. A. McGinnis, and S. Mitchell, *J. Chem. Soc.*, 286 (1944); (c) R. K. Hill, J. G. Martin, and W. H. Stouch, *J. Amer. Chem. Soc.*, **83**, 4006 (1961); (d) A. Schneider, R. W. Warren, and E. J. Janoski, *J. Org. Chem.*, **31**, 1617 (1966).

(4) W. H. Johnson, *J. Amer. Chem. Soc.*, **75**, 1498 (1953).

(5) J. L. Margrave, M. A. Frisch, R. G. Bautista, R. L. Clarke, and W. S. Johnson, *ibid.*, **85**, 546 (1963).

(6) N. L. Allinger, M. T. Tribble, M. A. Miller, and D. Wertz, *ibid.*, **93**, 1637 (1971).

(7) N. L. Allinger, B. J. Gorden, I. J. Tyminski, and M. T. Wuesthoff, *J. Org. Chem.*, **36**, 739 (1971).

(8) N. L. Allinger and J. L. Coke, *J. Amer. Chem. Soc.*, **82**, 2553 (1960).

TABLE I

PERHYDROANTHRACENE ISOMER DISTRIBUTIONS AT EQUILIBRIUM

		Percentage compositions			
		Temp, °C (times, hr)			
Isomer	Registry no.	198.5 (1634)	244.4[a] (195)	293.1 (93)	348.7 (66[b])
tst	1755-19-7	85.7	83.1	79.4	73.5
tat	30008-95-8	0.5	0.7	0.8	1.3
ct	29863-90-9	13.4	15.7	19.0	23.7
csc	19128-78-0	0.1	0.1	0.2	0.5
cac	29863-91-0	0.3	0.4	0.7	1.0

[a] Equilibrium may not have been reached. [b] Equilibrium was reached in less than 20 hr.

The experimental enthalpies and entropies were determined from a least-squares plot of $1/T$ *vs.* ln K, where K is the equilibrium constant between a given isomer and the most stable (tst) isomer. The results are summarized in Table II.

TABLE II

EXPERIMENTAL AND THEORETICAL THERMODYNAMIC PARAMETERS FOR THE PERHYDROANTHRACENES

Isomer	$\Delta H°_{exptl}$,[a,b] kcal/mol	$\Delta H°_{calcd}$,[b,c] kcal/mol	$\Delta S°_{exptl}$, eu	$\Delta S°_{theor}$,[d] eu
tst	0	0	0	0
ct	2.76 ± 0.28	2.62	+2.1 ± 0.6	+2.8
tat	4.15 ± 0.81	5.86	−1.6 ± 1.5	0
cac	5.58 ± 0.28	5.56	+0.3 ± 0.4	+1.4
csc	8.74 ± 0.61	8.13[e]	+4.0 ± 1.2	+2.2[f]

[a] The errors given are standard deviations. [b] The estimates made by Johnson from elementary ideas of conformational analysis are in very good agreement with these values. He estimated $\Delta H°$ as follows: tst, 0: ct, 2.4; cac, 4.8; tat, 5.6; csc, 6.4. The last value is based on a guess (a good one) by Pitzer regarding 1,3-dimethylcyclohexane: C. W. Beckett, K. S. Pitzer, and R. Spitzer, *J. Amer. Chem. Soc.*, 69, 2488 (1947). [c] Calculated as described in text. [d] Entropy calculated from symmetry and mixing only (see Table III). [e] Contains 0.27 kcal/mol additional owing to the boat form. [f] Contains an additional 0.8-eu entropy of mixing from the boat form.

Conformational Calculations.—Using our force field and previously described methodology, the relative enthalpy (at 25°) of each isomeric perhydroanthracene was calculated, and the relative entropies were calculated by considering the symmetry numbers and the meso or *dl* nature of the product. These quantities are summarized in Tables II and III. The heats of formation were calculated and are compared with the available experimental values in Table IV.

TABLE III

THEORETICAL ENTROPIES OF SYMMETRY AND MIXING FOR THE PERHYDROANTHRACENES

Isomer	Symmetry no.	ΔS_{symm}, eu	ΔS_{mixing}, eu	ΔS_{total}, eu	ΔS_{rel}, eu
tst	2 (meso)	−1.4	0	−1.4	0
ct	1 (*dl*)	0	+1.4	+1.4	+2.8
tat	4 (*dl*)	−2.8	+1.4	−1.4	0
cac	1 (meso)	0	0	0	+1.4
csc	1 (meso)	0	0	0	+1.4

TABLE IV

CALCULATED (FORCE FIELD) HEATS OF FORMATION FOR THE PERHYDROANTHRACENES (GAS PHASE, 25°)

Isomer	Calcd	Experimental
tst	−57.68	−58.13 ± 1.39
ct	−55.06	
tat	−51.82	−52.74 ± 1.47
cac	−52.04	
csc	−49.74[a]	

[a] Corrected for the presence of the boat conformation.

The entropies and enthalpies calculated and those measured experimentally are in reasonable agreement with one another. The errors listed in the tables are the standard deviations and measure only the scatter of the points, not the true probable errors which are probably twice as large.

Features of interest are as follows. The trans-syn-trans isomer is the most stable; the calculated and experimental heats of formation[5] (gas phase) are respectively −57.68 and −58.13 ± 1.39 kcal/mol; so the agreement is excellent. The cis-trans is the next most stable isomer, and one which exists in fairly large amount in the equilibrium mixture. The relative thermodynamic quantities can therefore be measured fairly accurately for this isomer, and the agreement between the calculations and experiment is fair (note the calculations are for the gas phase, while the equilibrium is measured in the liquid). The tat isomer necessarily has the center ring in a boat (twist) form, and the calculated and (gas phase) heats of formation are again in good agreement. In analogy to other boat forms,[9] it might be thought the entropy would be larger than indicated by symmetry considerations, but this does not prove to be the case. The fusion of the boat between two chairs restricts its mobility somewhat, which may be the reason.

The cis-anti-cis isomer has a calculated enthalpy which is in good agreement with experiment. The agreement between the entropies is marginal.

The cis-syn-cis isomer is perhaps the most interesting, because the experimental enthalpy has not been previously known; Johnson's value is only an estimate. The calculated and experimental values are in good agreement. The experimental entropy is larger than expected from the single stable chair conformation, which has a bad syn diaxial interaction that can be relieved if the center ring assumes a boat form. The calculated energy of this form is 2.07 kcal/mol above that of the chair. It is therefore in equilibrium with the chair to the extent of 13% at 271°. The presence of the boat form raises the enthalpy of the compound somewhat (0.27 kcal/mol), and raises the entropy appreciably (0.8 eu). It may be that smaller amounts of other conformations of higher energy increase both the enthalpy and the entropy of the compound at these elevated temperatures, but we have not investigated this possibility.

We believe the calculated heats of formation and the

(9) N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.*, **82**, 2393 (1960).

TABLE V

THE THERMODYNAMIC QUANTITIES FOR THE PERHYDROANTHRACENES

Isomer	$\Delta H°_{exp}$	$\Delta S°_{exp}$	$T\Delta S°_{exp}$	$\Delta G°_{exp}$[a]	$\Delta H°_{calcd}$	$\Delta S°_{calcd}$	$T\Delta S°$	$\Delta G°_{calcd}$[a]
tst	0	0	0	0	0	0	0	0
ct	+2.76	+2.1	+1.14	+1.62	2.62	+2.8	+1.52	+1.10
tat	+4.15	−1.6	−0.87	+5.02	5.86	0	0	+5.86
cac	+5.58	+0.3	+0.16	+5.42	5.56	+1.4	+0.76	+4.80
csc	+8.74	+4.0	+2.18	+6.56	8.13	+2.2	+1.20	+6.93

[a] 544 °K.

differences between them are accurate to better than 1 kcal/mol, and the experimental results are in accord with this. Finally, the free energies are given in Table V.

Acknowledgment.—We are indebted to Dr. R. L. Clarke for furnishing us with the samples of the perhydroanthracenes used for identification purposes in this work.

A New Approach to the Synthesis of Dibenzo[a,l]pyrenes[1,2]

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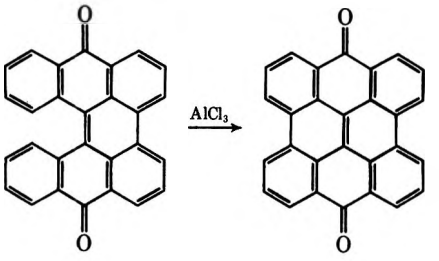
A new method for the synthesis of dibenzo[a,l]pyrene and various derivatives has been achieved through an application of the Scholl reaction. The key to the new approach is to use 1-arylbenz[a]anthracenes as the precursors to the desired polycyclic aromatic compounds. The parent hydrocarbon and derivatives containing alkyl, halogen, and alkyoxyl substituents have been prepared as well as the corresponding TNF adducts.

The Scholl reaction,[5] which is the elimination of two aryl-bound hydrogen atoms accompanied by the formation of a new aryl–aryl bond under the influence of a Friedel–Crafts catalyst, has been known for some time. This type of reaction was first observed by Friedel and Crafts who reported the formation of biphenyl from benzene in the presence of aluminum chloride; Homer[6] also reported the formation of dinaphthyl from naphthalene in the presence of aluminum chloride. It was Scholl who, after publishing the synthesis of *meso*-naphthodianthrone (2)[7] from helianthrone (1) using aluminum chloride as the dehydrogenating catalyst, and the



1 2

formation of perylene by three different methods,[8] recognized the potentiality and generality of this reaction. Subsequent to extensions of the reaction by Scholl himself,[9] no important contributions to the Scholl reaction were published until 1950 when Baddely[10] showed that many reactions effected by aluminum chloride and other Friedel–Crafts reagents do not occur in the absence of hydrogen chloride or traces of water. The next and perhaps most significant contribution to the understanding of the Scholl reaction is in the paper of Nenitzescu and Balaban[5] in which they propose that the reaction takes place in three steps: first, a protonation; second, an electrophilic substitution; and finally, a dehydrogenation to yield the final aromatic product.

The suggestion of Nenitzescu and Balaban[5] that the first step in the Scholl reaction is a protolytic reaction yielding a σ complex is well supported.[11] The fact that Scholl reactions occur readily and in high yield when electron-rich positions are involved but fail when the reaction has to take place at electron-poor positions supports the idea that the second step in Nenitzescu and Balaban's mechanism is one of electrophilic substitution. The cyclodehydrogenation of 8-(1-naphthyl)benz[a]anthracene to naphtho[2,1-a]perylene[12] proceeds readily and in good yield, presumably because an electron-rich position undergoes electrophilic attack. However, benzophenone does not yield fluorenone[9a] under Scholl reaction conditions nor does 1,5-dibenzoylnaphthalene[9e] undergo a Scholl reaction. Both reactions fail presumably because an electrophilic attack would have to occur into a position deactivated by

(1) Presented before the Division of Organic Chemistry at the Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Fla., Dec 1968.

(2) This investigation was supported by a research grant, AP-00088-06, from the Division of Air Pollution, Bureau of State Services, U. S. Public Health Service.

(3) Department of Chemistry, Northeast Louisiana University, Monroe, La. 71201.

(4) Abstracted in part from the Doctorate thesis of J. Yanez, presented to the Virginia Polytechnic Institute, 1966.

(5) C. D. Nenitzescu and A. T. Balaban, "Friedel–Crafts and Related Reactions," Vol. II, G. A. Olah, Ed., Interscience, New York, N. Y., 1964, p 979.

(6) A. Homer, *J. Chem. Soc.*, 1103 (1907).

(7) R. Scholl and J. Mansfeld, *Ber.*, **43**, 1734 (1910).

(8) R. Scholl, C. Seer, and R. Weitzenbock, *ibid.*, **43**, 2202 (1910).

(9) (a) R. Scholl and C. Seer, *Justus Liebigs Ann. Chem.*, **394**, 111 (1912); (b) R. Scholl and C. Seer, *Ber.*, **55**, 109 (1922); (c) R. Scholl and G. Schwarzer, *ibid.*, **55**, 324 (1922); (d) R. Scholl and C. Seer, *ibid.*, **55**, 330 (1922); (e) R. Scholl and H. Neumann, *ibid.*, **55**, 118 (1922).

(10) B. Baddely, *J. Chem. Soc.*, 994 (1950).

(11) H. C. Brown and H. Pearsall, *J. Amer. Chem. Soc.*, **74**, 191 (1952); D. A. McCaulay and A. P. Lien, *ibid.*, **73**, 2013 (1951); D. A. McCaulay, B. H. Schoemaker, and A. P. Lien, *Ind. Eng. Chem.*, **42**, 2103 (1950); G. A. Olah and J. J. Kuhn, *J. Amer. Chem. Soc.*, **80**, 6535 (1958); G. A. Olah, H. W. Quinn, and J. J. Kuhn, *ibid.*, **82**, 426 (1960); P. Kovacic and A. Kyriakis, *ibid.*, **85**, 454 (1963).

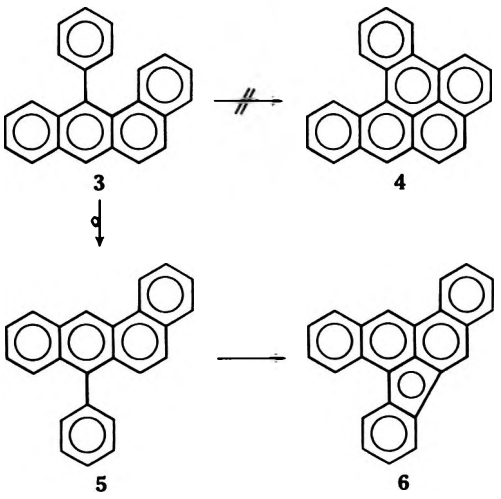
(12) F. A. Vingiello, W. W. Zajac, Jr., and L. G. Mahone, *J. Org. Chem.*, **28**, 3253 (1963).

a carbonyl group. Evidence to support the idea that the last step is the actual dehydrogenation step has been difficult to obtain. Indeed, it has been difficult to account for the fate of the hydrogen lost in the Scholl reaction. Since only a small amount of hydrogen is evolved during the reaction,[13] it is evident that hydrogen is consumed in reductive processes. One interesting example where the dihydro intermediate was isolated is afforded by the Scholl reaction on 7-phenyldibenz[*a*,*h*]anthracene which gave 10a,10b-dihydrobenzo[*e*]naphtho[1,2-*b*]pyrene which was isolated, characterized, and then dehydrogenated to benzo[*e*]naphtho[1,2-*b*]pyrene.[14]

Results

The approach to the synthesis of dibenzo[*a*,*l*]pyrene (**4**), using the Scholl reaction, has been to dehydrogenate 12-phenylbenz[*a*]anthracene (**3**)[15] (Scheme I).

SCHEME I



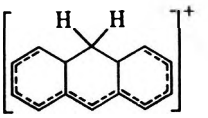
Using Clar's procedure[15] the cyclodehydrogenation of the three isomeric 12-monomethylphenylbenz[*a*]anthracenes[16] and the six 12-dimethylphenylbenz[*a*]anthracenes[16] was performed, and it was concluded that derivatives of dibenzo[*a*,*l*]pyrene had been synthesized. The structural assignments were based largely on the ultraviolet spectra, which were similar to those reported by Clar[15] for dibenzo[*a*,*l*]pyrene, and on the elemental analyses. Yields in all the above-mentioned reactions were poor.

Later Lavit-Lamy and Buu Hoi[17] showed conclusively that what had been reported as dibenzo[*a*,*l*]-pyrene[15] was actually dibenzo[*a*,*e*]fluoranthene (**6**). They synthesized **6** independently and showed it to be identical with what had been reported as **4**. They also suggested that the other[16] "dibenzo[*a*,*l*]pyrenes," since they were made by a similar method, were also in reality dibenzo[*a*,*e*]fluoranthenes.[18] It was suggested[17] that **3** rearranged to **5** which then gave **6**. This suggestion was later verified experimentally.[19]

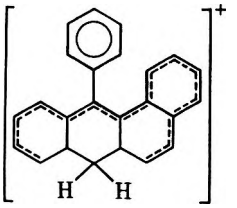
(13) G. D. Buckley, *J. Chem. Soc.*, 561 (1945).
(14) F. A. Vingiello and P. D. Henson, *J. Org. Chem.*, **30**, 2842 (1965).
(15) E. Clar and D. Stewart, *J. Chem. Soc.*, 687 (1951).
(16) F. A. Vingiello and W. W. Zajac, Jr., *J. Org. Chem.*, **26**, 2228 (1961).
(17) D. Lavit-Lamy and N. P. Buu Hoi, *Chem. Commun.*, 92 (1966).
(18) A manuscript is being prepared wherein experimental data which verify this suggestion will be presented.
(19) F. A. Vingiello and A. K. Youssef, *Chem. Commun.*, 863 (1967).

A thorough study of literature on the Scholl reaction suggested to us reasons why **3** failed to give **4** and also led us to propose a new route to **4** *via* the Scholl reaction.

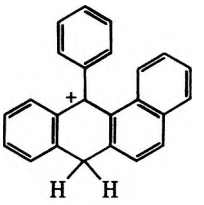
Moist aluminum chloride is able to protonate aromatic systems to form σ complexes.[11,20] Gold and Tye[21] and Gold and Long[22] confirmed that protonation of anthracene takes place at a meso position and that the σ complex may be represented as follows.



We now suggest, by way of analog, that **3** is protonated by moist aluminum chloride to give a σ complex which may be represented as follows.[23]



Although the positive charge is distributed throughout the benz[*a*]anthracene system, its localization at the 12 position is probably favored over the 1 position since this would provide structure **7** in which Kekulé structures could be achieved in the benzene and naphthalene portions of the benz[*a*]anthracene structure. It would

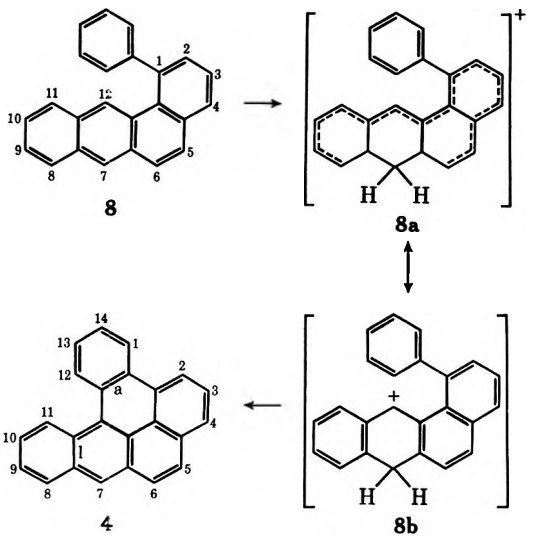


seem then that **3** is a poor precursor for the preparation of **4** *via* a Scholl reaction since (a) the likely intermediate is not favorably disposed to an electrophilic substitution, that is, attack by C-1 of **7** on the phenyl ring; and (b) the phenyl ring in **3** is sterically hindered because of interference between the hydrogen atom at C-1 and the ortho hydrogen atoms on the phenyl ring. These considerations are consistent with the fact that **3** does not give **4** but rearranges to **5**, where the phenyl ring is better accommodated, and then gives **6**.[17]

It appeared to us, based on the above considerations, that 1-phenylbenz[*a*]anthracene (**8**) would be an excellent precursor for conversion to dibenzo[*a*,*l*]pyrene *via* a Scholl reaction. On treatment with moist aluminum chloride, **8** would be expected to form the σ complex **8a**. The complex in what is probably its most stable form, **8b**, is well disposed for an intramolecular

(20) W. E. Truce, *J. Amer. Chem. Soc.*, **74**, 4721 (1952).
(21) V. Gold and F. C. Tye, *J. Chem. Soc., London*, 2172 (1952).
(22) V. Gold and F. A. Long, *J. Amer. Chem. Soc.*, **75**, 4543 (1953).
(23) It should be noted that the phenyl ring is restrained from entering into coplanarity with the benz[*a*]anthracene moiety; see, for example, R. N. Jones, *ibid.*, **67**, 2127 (1945).

electrophilic substitution reaction involving the C-12 atom and an ortho position of the phenyl ring leading finally to dibenzo[a,l]pyrene. The phenyl ring in **8** is also less hindered than it is in **3** and should be less prone to migrate. Indeed, when **8** was subjected to Scholl reaction conditions, **4** was easily isolated in excellent



yield. When a methyl group was substituted in the phenyl ring of **8** at position 3 or 4, the resulting compounds easily gave the expected methyldibenzo[a,l]pyrenes when subjected to Scholl reaction conditions. Attempts to prepare 1-(2-tolyl)-3,4-dihydrobenz[a]anthracene for this study met with failure. The Grignard reagent of *o*-bromotoluene does not couple with 1-keto-1,2,3,4-tetrahydrobenz[a]anthracene (**9**) because of the steric hindrance of the bulky methyl group which interferes with the OMgBr group. In the Scholl reaction the methyl group probably makes the electrophilic attack by the intermediate carbonium ion on the phenyl ring easier because of its electron-release properties.

When 1- and 4-halophenylbenz[a]anthracenes were prepared and subjected to Scholl reaction conditions, substantial evidence was obtained to support the proposed mechanism. The bromine atom in **20** has no appreciable deactivating effect on the position of cyclization. Hence the cyclodehydrogenation occurs in good yield in a reaction time of 5 min. The chlorine atom in **21** deactivates the position of cyclization to a substantial degree by a $-I$ effect. The time needed to effect cyclization of **21** to give **27** is 2 hr. It would appear that the flourine atom of **22** deactivates the position of cyclization tremendously since the reaction required 12 hr to effect cyclization.[24]

Attempts at isolating 13-methoxydibenzo[a,l]pyrene from **23** under Scholl reaction conditions failed. When the methoxy group lies meta to the point of cyclization, this position is extremely deactivated due to the $-I$ effect. Reaction times of 2 hr or less gave only the starting material **23**. Longer reaction times produced tars, probably because of the fact that the methoxy group is cleaved to the reactive phenolic species.

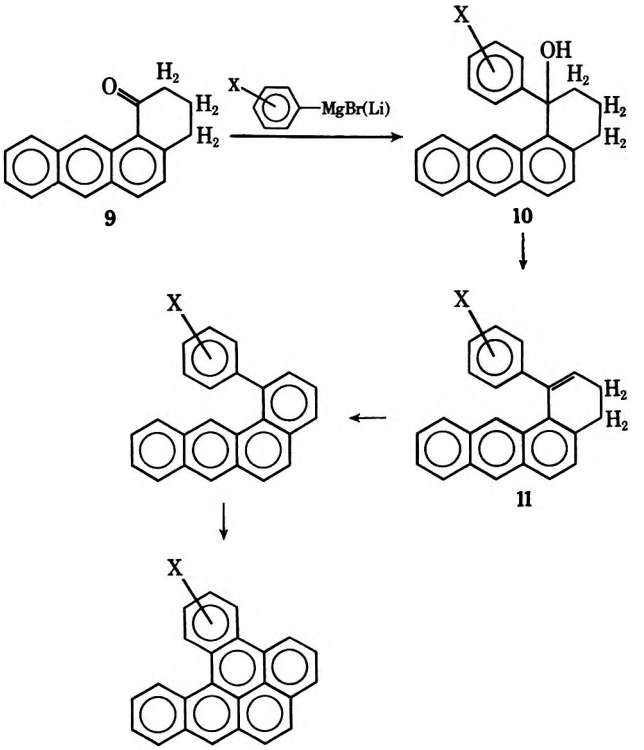
(24) When 1-pyridylbenz[a]anthracenes were prepared and subjected to Scholl reaction conditions, no dehydrogenation occurred. Apparently the pyridyl ring presents an extremely electron-poor structure for the carbonium ion to attack and the reaction fails; see ref 4 for details.

Experimental Section[25,26]

1-Phenyl-3,4-dihydrobenz[a]anthracene (11, X = H).—By using 15.7 g (0.10 mol) of bromobenzene in 125 ml of anhydrous ether and 2.4 g (0.10 g-atom) of magnesium turnings, a Grignard reagent was formed in the usual way. After the magnesium had been consumed, the ether was replaced by anhydrous benzene; the resulting benzene solution was cooled to ice bath temperature. A solution of 2.5 g (0.010 mol) of 1-keto-1,2,3,4-tetrahydrobenz[a]anthracene (**9**) in 50 ml of anhydrous benzene was added slowly to the cold solution. The resulting solution was stirred for 36 hr. The reaction mixture was then hydrolyzed with 50 ml of 10% HCl. The layers were separated; the aqueous layer was extracted once with 50 ml of benzene. The combined benzene layers were washed twice with 50-ml portions of water and dried over magnesium sulfate. The dry solution was concentrated to about 25 ml; an infrared spectrum of the solution showed the presence of a hydroxyl function. The solvent was removed completely and the resulting oil heated at 70° in a vacuum oven for 18 hr. The oil was dissolved in benzene; an infrared spectrum of the solution showed that the hydroxyl band had disappeared. Addition of ethanol to the solution caused crystallization to occur, 2.0 g (67% yield). Recrystallization gave yellow needles, mp 145–148°. The crystals were dissolved in a small amount of benzene and absorbed on an acid alumina column. A colorless, blue fluorescing band was removed using a 1:4 benzene–petroleum ether solution. Upon concentration of this first fraction, a yellow oil resulted which was crystallized from a benzene–ethanol mixture as yellow needles. Recrystallization from benzene–ethanol gave yellow needles, mp 145–147°.

The remaining new 1-phenyl-3,4-dihydrobenz[a]anthracenes were prepared essentially as was compound **11** as illustrated in Scheme II. The data are shown in Table I.

SCHEME II



1-Phenylbenz[a]anthracene (8).—A solution of 1.0 g (0.003 mol) of 1-phenyl-3,4-dihydrobenz[a]anthracene in 75 ml of anhydrous benzene was added to 1.0 g of 2,3-dichloro-5,6-dicyanobenzoquinone which had been placed in a 100-ml round-bottom flask equipped with a reflux condenser. The reaction mixture was allowed to reflux for 4 hr. The cold solution was extracted with 10% sodium hydroxide solution until most of the

(25) All melting points were taken on a Fisher–Johns melting point block and are corrected.

(26) Analyses for C, H, and N were performed in this laboratory; halogen analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

TABLE I

NEW 1-PHENYL-3,4-DIHYDROBENZ[a]ANTHRACENES[a]

Compd	Yield, %	Mp, °C
1-Phenyl-3,4-dihydrobenz[a]-anthracene (11)	67	145–147
1-(4-Tolyl)-3,4-dihydrobenz[a]-anthracene (12)	62	166–168
1-(3-Tolyl)-3,4-dihydrobenz[a]-anthracene (13)	40	135–137
1-(4-Bromophenyl)-3,4-dihydrobenz-[a]anthracene (14)[b]	40	228.5–229.5
1-(4-Chlorophenyl)-3,4-dihydrobenz-[a]anthracene (15)	66	223.5–224
1-(4-Fluorophenyl)-3,4-dihydrobenz-[a]anthracene (16)	68	184.5–185.5
1-(4-Methoxyphenyl)-3,4-dihydrobenz-[a]anthracene (17)	61	185–186

[a] All compounds in Tables I–IV (except compound 31) gave satisfactory C and H analytical data (±0.4). In addition, compounds in Tables I–IV which contain halogen gave satisfactory halogen analyses and all compounds in Table IV (except compound 31) gave satisfactory N analyses. All analytical data were made available to the editors and the referees. [b] Prepared by the reaction of *p*-bromophenyllithium with 1-keto-1,2,3,4-tetrahydrobenz[a]anthracene.

yellow color had disappeared. The solution was then washed with water and dried over anhydrous magnesium sulfate. The dry benzene solution was concentrated to about 10 ml and 25 ml of 95% ethanol was added. The resulting solution was then concentrated until crystals began to appear; then enough benzene was added to dissolve the crystals. The product crystallized as long white needles and was isolated in 90% yield (0.90 g), mp 157–158°.

The remaining new 1-phenylbenz[a]anthracenes were prepared essentially as was compound **8**. The data are shown in Table II.

TABLE II

NEW 1-PHENYLBENZ[a]ANTHRACENES

Compd	Yield, %	Mp, °C
1-Phenylbenz[a]anthracene (8)	90	157–158
1-(4-Tolyl)benz[a]anthracene (18)	86	152–153
1-(3-Tolyl)benz[a]anthracene (19)	80	131–132
1-(4-Bromophenyl)benz[a]-anthracene (20)	78	168.5–169.5
1-(4-Chlorophenyl)benz[a]-anthracene (21)	83	164–165
1-(4-Fluorophenyl)benz[a]-anthracene (22)	88	158–159
1-(4-Methoxyphenyl)benz[a]-anthracene (23)	85	140.5–141.5

Dibenzo[a,l]pyrene (4).—To a refluxing mixture of 25 ml of anhydrous benzene, 0.6 g of aluminum chloride, and 0.5 g of stannic chloride was added a hot solution of 0.30 g of 1-phenylbenz[a]anthracene in 25 ml of anhydrous benzene. The reaction mixture which immediately turned green was allowed to reflux for 5 min. The reaction mixture was slowly poured into 500 ml of 10% hydrochloric acid. The layers were separated; the acid layer was extracted with 50 ml of benzene. The combined benzene solutions were washed with water and dried over anhydrous magnesium sulfate. The dry solution was concentrated to about 5 ml. The addition of 95% ethanol precipitated a tan solid. The solid, 0.20 g (66% yield), melting at 160–163°, was recrystallized from a benzene–ethanol mixture as pale yellow plates, mp 162–163°.

The remaining new dibenzo[a,l]pyrenes were prepared essentially as was compound **4**. The data are shown in Table III.

TABLE III

NEW DIBENZO[a,l]PYRENES

Compd	Yield, %	Mp, °C
Dibenzo[a,l]pyrene (4)	66	162–163
13-Methyldibenzo[a,l]pyrene (24)	57	180–181
14-Methyldibenzo[a,l]pyrene (25)	66	164–165
13-Bromodibenzo[a,l]pyrene (26)	52	216–217
13-Chlorodibenzo[a,l]pyrene (27)	54[a]	212–213
13-Fluorodibenzo[a,l]pyrene (28)	58[b]	185–186

[a] After 2-hr reaction time. [b] After 12-hr reaction time.

2,4,7-Trinitrofluorenone Adduct of Dibenzo[a,l]pyrene (29).—A hot solution of 0.050 g (0.00016 mol) of dibenzo[a,l]pyrene in 5 ml of benzene was added to a hot solution of 0.0504 g (0.00016 mol) of 2,4,7-trinitrofluorenone (TNF) in 10 ml of ethanol. The mixture darkened immediately; brown-green needles began to form as soon as the solution began to cool. The product was recrystallized from a benzene–ethanol mixture, mp 218–219°.

The remaining TNF adducts were prepared essentially as was compound **29**. The data are shown in Table IV.

TABLE IV

NEW TNF ADDUCTS OF DIBENZO[a,l]PYRENES (NEW DIBENZO[a,l]PYRENE–TNF ADDUCTS)

Compd	Color	Mp, °C
Dibenzo[a,l]pyrene–TNF adduct (29)	Brown-green	218–219
13-Methyldibenzo[a,l]pyrene–TNF adduct (30)	Brown	220–221
14-Methyldibenzo[a,l]pyrene–TNF adduct (31)	Green	
13-Bromodibenzo[a,l]pyrene–TNF adduct (32)	Brown	226.5–227.5
13-Chlorodibenzo[a,l]pyrene–TNF adduct (33)	Brown	226–227
13-Fluorodibenzo[a,l]pyrene–TNF adduct (34)	Brown	205–205.5

Registry No.—**4**, 191-30-0; **8**, 10383-87-6; **11**, 29568-49-8; **12**, 29568-50-1; **13**, 29568-51-2; **14**, 29568-52-3; **15**, 29568-53-4; **16**, 29568-54-5; **17**, 29584-23-4; **18**, 29584-24-5; **19**, 29584-25-6; **20**, 29584-26-7; **21**, 29584-27-8; **22**, 29584-28-9; **23**, 29584-29-0; **24**, 5950-67-4; **25**, 5950-66-3; **26**, 29584-32-5; **27**, 29584-33-6; **28**, 29584-34-7; **29**, 29584-35-8; **30**, 29584-36-9; **32**, 29584-37-0; **33**, 29584-38-1; **34**, 29584-39-2.

Synthesis of *exo*- and *endo*-Tetracyclo[5.4.0.0^{2,4}.0^{3,6}]undeca-1(7),8,10-trien-5-ol and Related Derivatives[1]

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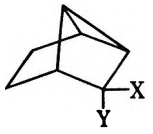
Both *exo*- and *endo*-tetracyclo[5.4.0.0^{2,4}.0^{3,6}]undeca-1(7),8,10-trien-5-ol were synthesized by stereospecific pathways involving the photochemically induced rearrangement of appropriately substituted benzonorbornadienes. Derivatives of the tetracyclic compounds were prepared and some of the chemistry of this system is reported.

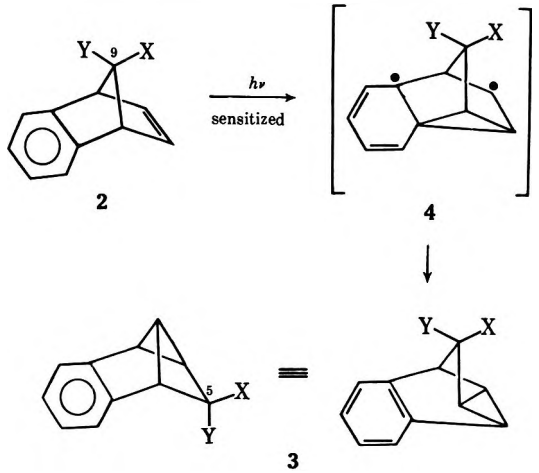
Our recently reported[2] synthesis of *endo*-tricyclo[3.2.0.0^{2,7}]heptan-6-ol (**1a**) and subsequent investigation[3] of the remarkable solvolytic reactivity of some of



1a, X = H; Y = OH
b, X = OH; Y = H

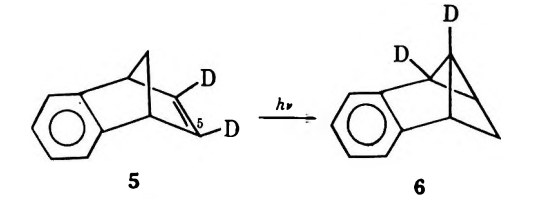
its derivatives have spurred our interest in related systems incorporating the essential features of **1**. We became especially interested in determining the exo/endo rate ratio for the 6-substituted tricyclic system (*i.e.*, **1a** and **1b**).

The reported[4] sensitized photorearrangement of benzonorbornadiene (**2**, X = Y = H) to the benzotricyclic hydrocarbon **3** (X = Y = H) has been suggested to proceed through a diradical intermediate **4** (X = Y = H).[5] This pathway suggests a potential stereospecific approach to both *exo*- and *endo*-tetracyclo[5.4.0.0^{2,4}.0^{3,6}]undeca-1(7),8,10-trien-5-yl derivatives (*i.e.*, **3**).

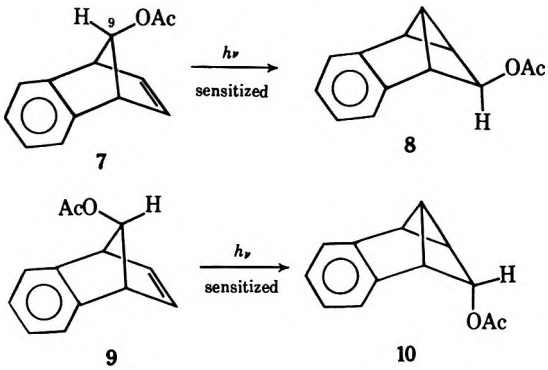


2 **4** **3**

The observed[4b] stereospecificity of the photorearrangement of the dideuteriobenzonorbornadiene **5** to **6** is expected on the basis of a diradical corresponding to **4**. Moreover, such stereospecificity in related photorearrangements is well precedented.[6] These results suggest that an effective route to *exo*- and *endo*-tetracyclo[5.4.0.0^{2,4}.0^{3,6}]undeca-1(7),8,10-trien-5-yl derivatives would involve photorearrangement of the appropriate 9-substituted benzonorbornadiene, **2**. Thus, the acetophenone-sensitized photorearrangement of *anti*-9-acetoxybenzonorbornadiene (**7**) is expected to afford exo benzotricyclic acetate **8**, while *syn*-9-acetoxybenzonorbornadiene (**9**) should give endo benzotricyclic acetate **10**. We set out to confirm these predictions.



5 **6**



7 **8** **9** **10**

***exo*-Tetracyclo[5.4.0.0^{2,4}.0^{3,6}]undeca-1(7),8,10-trien-5-yl Acetate.**—Benzonorbornadiene[7] was converted into *anti*-9-*tert*-butoxybenzonorbornadiene (**11**)[8a] as reported. Acid-catalyzed ether cleavage of **11** in acetic acid–acetic anhydride[8] containing perchloric acid affords *anti*-9-acetoxybenzonorbornadiene[8a,9] (**7**) in 80% yield. The nmr spectrum of **7** is in accord with that reported.[8a] A 1% solution of anti acetate **7** in hexane was photolyzed in the presence of acetophenone to give exo benzotricyclic acetate **8** (95% yield).

(1) We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(2) J. J. Tufariello, T. F. Mich, and R. J. Lorence, *Chem. Commun.*, 1202 (1967).

(3) J. J. Tufariello and R. J. Lorence, *J. Amer. Chem. Soc.*, **91**, 1546 (1969).

(4) (a) J. P. Edman, *ibid.*, **88**, 3454 (1966); (b) J. R. Edman, *ibid.*, **91**, 7103 (1969).

(5) It is clear that this rearrangement may be concerted in nature: R. B. Woodward and R. Hoffman, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

(6) (a) H. Hart and R. K. Murray, Jr., *J. Amer. Chem. Soc.*, **91**, 2183 (1969); (b) R. C. Hahn, L. V. Rothman, *ibid.*, **91**, 2409 (1969); (c) H. E. Zimmerman and C. O. Bender, *ibid.*, **91**, 7516 (1969), and references cited therein: (d) M. G. Waite, G. A. Sim, C. R. Orlander, R. J. Warnet, and D. M. S. Wheeler, *ibid.*, **91**, 7763 (1969).

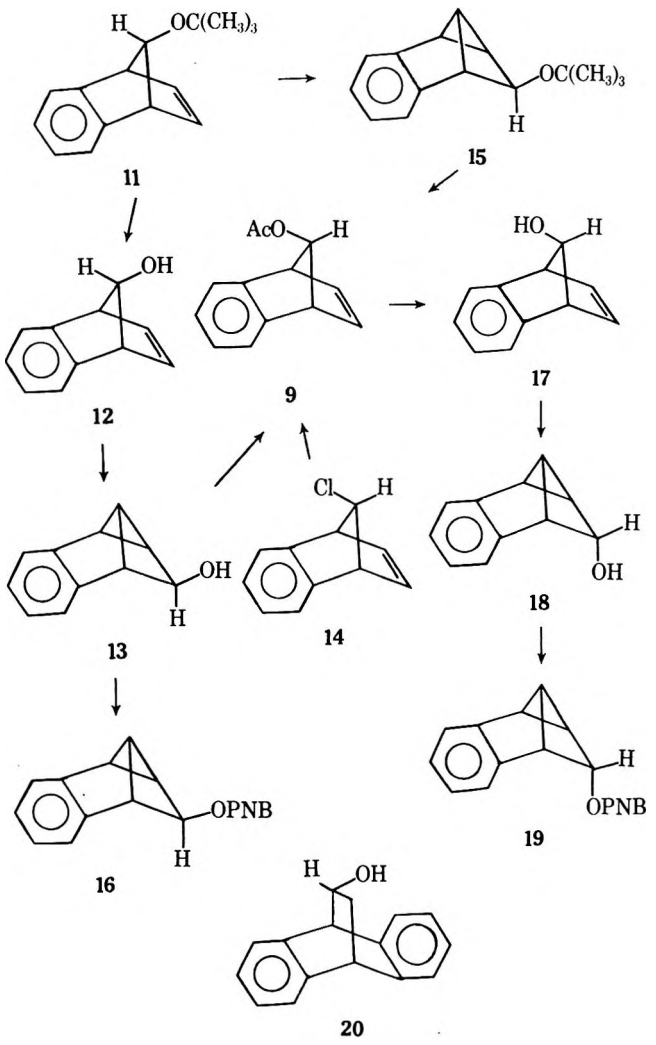
(7) G. Wittig and E. Knauss, *Chem. Ber.*, **91**, 895 (1958); (b) L. Friedman and F. M. Logullo, *J. Amer. Chem. Soc.*, **85**, 1549 (1963); (c) T. F. Mich, E. J. Nienhouse, T. F. Farina, and J. J. Tufariello, *J. Chem. Educ.*, **45**, 272 (1968).

(8) (a) M. E. Brennan and M. A. Battiste, *ibid.*, **32**, 324 (1968); (b) P. R. Story, *J. Org. Chem.*, **26**, 287 (1961).

(9) S. J. Cristol and G. W. Nachtigall, *ibid.*, **32**, 3727, 3738 (1967).

The exo-5-substituted benzotricyclic system was also obtained by conversion of the anti *tert*-butyl ether **11** to the corresponding anti alcohol **12** using the method of Brennan and Battiste,[8a] followed by photolysis to afford exo benzotricyclic alcohol **13** (Scheme I). This

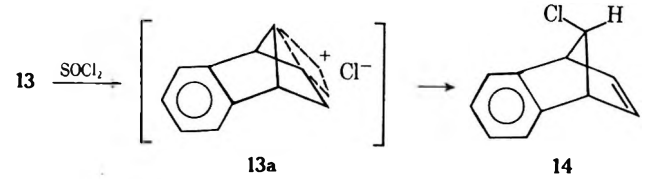
SCHEME I



alcohol was also prepared by lithium aluminum hydride reduction of the exo acetate **8**.

The nmr spectrum of benzotricyclic hydrocarbon **3** (X = Y = H) contains a doublet (J = 2.5 Hz) for the endo hydrogen (*i.e.*, Y in **3**) when decoupled at the frequency of the exo proton (*i.e.*, X in **3**). In addition, studies of 8,11-disubstituted tetracyclo[5.4.0.0^{2,4}.0^{3,6}]-undeca-1,8,10-trienes reveal a similar value (J = 2.7 Hz) for this coupling constant.[6d] The exo benzotricyclic acetate **8** exhibited the expected doublet for H-5 (J = 4 Hz) at δ (CCl_4, TMS) 4.07 ppm.

The exo acetate **8** was reduced to the corresponding exo benzotricyclic alcohol **13**, which in turn was transformed into the known *syn*-9-chlorobenzonorbornadiene[10] (**14**) with thionyl chloride in ether. The observed stereospecificity of this reaction is explicable on the basis of an exclusive collapse of the presumed ion-pair intermediate **13a** to give the observed syn chloride **14**. Cristol and Nachtigall[10] have shown that carbonium ions such as **13a** undergo nucleophilic attack to afford syn products exclusively.



The syn chloride **14** was transformed into the *syn*-9-acetoxybenzonorbornadiene (**9**) by solvolysis in acetic acid containing potassium acetate.[10] The spectral and physical properties of **14** and **9** are in accord with those previously reported[8a,9,10] as is the observed stereospecificity of the **14** → **9** transformation. In addition, the exo benzotricyclic alcohol **13** can be directly transformed into syn acetate **9** by treatment with acetic anhydride in acetic acid containing perchloric acid.

The acetophenone-sensitized photolysis of *anti*-9-*tert*-butoxybenzonorbornadiene (**11**) in hexane affords exo *tert*-butyl ether **15**. Rearrangement of **15** in acetic acid (*cf.* Experimental Section) gave syn acetate **9** in good yield. This latter process (*i.e.*, **11** → **15** → **9**) provides a most convenient and efficient means of obtaining the syn acetate **9**. In addition, this brief sequence, involving a tricyclic intermediate, appears to be a remarkably facile means for bridging the anti and syn benzonorbornadienyl series.

All the exo benzotricyclic derivatives (*i.e.*, the *tert*-butyl ether **15**, acetate **8**, and *p*-nitrobenzoate **16**), with the exception of the alcohol, exhibit a doublet assignable to the endo-5 hydrogen. In the alcohol this signal is complicated by the presence of further coupling of the hydroxyl proton to H-5. Observation of models indicates that the endo-5 hydrogen in the exo-alcohol **13** is shielded as a result of the anisotropic effect of the benzene ring in **13** and consequently appears at higher field (δ 3 52 ppm) than that observed for the corresponding exo-5 hydrogen in the endo alcohol **18** (δ 4.22 ppm).

***endo*-Tetracyclo[5.4.0.0^{2,4}.0^{3,6}]undeca-1(7)8,10-trien-5-yl Acetate.**—The acetophenone-sensitized photorearrangement of *syn*-9-acetoxybenzonorbornadiene (**9**) gives endo benzotricyclic acetate **10** in 92% yield. Reduction of the acetate **10** with lithium aluminum hydride affords the endo alcohol **18**, which was converted into its *p*-nitrobenzoate **19**. The nmr spectrum of the acetate displayed the exo-5 hydrogen as the anticipated quartet[11] at δ (CCl_4, TMS) 5.19 ppm (J = 7.5 Hz, J = 4 Hz). The *p*-nitrobenzoate exhibited the corresponding quartet at δ (CCl_4, TMS) 5.47 ppm (J = 6.8 Hz, J = 3.3 Hz). An alternative procedure employed for the synthesis of the endo alcohol **18** involves the complex metal hydride reduction of the syn acetate **9** to the corresponding alcohol **17**, which may then be photolyzed as usual to give **18**.

The structures of the exo and endo alcohols, **13** and **18** respectively, were further confirmed by the results of intramolecular hydrogen-bonding studies in the first overtone region for hydroxyl stretching in the near infrared. For those compounds which exhibit two absorptions in this region, the absorption at the shorter wavelength (*ca.* 14100 Å) is attributable to free hydroxyl while that at longer wavelength may be fairly safely attributed to intramolecularly hydrogen-bonded hydroxyl provided that $B_1/B_2 < 1$ and $\Delta\nu/2 > 26$ cm^{-1} (*cf.*

(10) S. J. Cristol and G. W. Nachtigall, *J. Amer. Chem. Soc.*, **90**, 7132, 7133 (1968).

(11) (a) H. Tanida, T. Tsuji, and T. Irie, *ibid.*, **88**, 864 (1966); (b) A. Diaz, M. Brookhart, and S. Winstein, *ibid.*, **88**, 3133 (1966).

TABLE I
HYDROGEN-BONDING STUDIES[a]

Compd[b]	λ_{max}, Å	B, cm mol^{-1} [c]	B_1/B_2[d]	$\Delta\nu/2$,[e] cm^{-1}
Exo alcohol **13**	14158	59.2	2.30	25
	14257	27.7		
Endo alcohol **18**	14150	32.0	0.57	36
	14306	56.5		
Dienol **20**	14161	51.0	0.57	37
	14310	90.4		

[a] The procedure used is described in the Experimental Section (*cf.* ref 12). [b] All compounds were studied over a range in concentrations (*i.e.*, 10^{-1} to 10^{-3} *M*) in carbon tetrachloride. [c] The areas of the peaks were determined by using $B = \epsilon \times \Delta\nu_{1/2}$, where ϵ (cm^2 mol^{-1}) is the extinction coefficient and $\Delta\nu_{1/2}$ is the peak width at half-height in reciprocal centimeters. [d] The ratio of the peak areas (B_1/B_2) was determined by inserting the area of the lowest wavelength absorption in the numerator. [e] The peak separation $\Delta\nu/2$ includes the factor 2 since we are dealing with the first overtone region for hydroxyl stretching.

Table I).[12] These criteria are clearly met for the endo alcohol **18** where intramolecular hydrogen bonding to the proximate benzene ring is expected to occur, especially on comparison with dibenzobicyclo[2.2.2]octadienol **20**. In the case of the exo alcohol **13**, where the aforementioned criteria are not met, the possibility of intramolecular hydrogen bonding can not be distinguished from that where the two absorptions are due to the presence of two (or more) conformations involving the hydroxyl group, each conformation having a somewhat different hydroxyl stretching frequency.[12] Thus, while it is tempting to postulate a weak hydrogen-bonding interaction to the cyclopropane ring in the exo isomer **13**, this conclusion is not warranted.

The synthesis of the exo and endo alcohols **13** and **18**, and their respective *p*-nitrobenzoate derivatives **16** and **19**, makes possible a study of their respective chemical reactivities.

Experimental Section

All melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-5a spectrophotometer and calibrated using the 6.238-μ bond of polystyrene. Proton nmr spectra were obtained using TMS as internal standard on a Varian A-60 or Varian HA-60 spectrometer.

Benzonorbornadiene (2, X = H; Y = H).—The previously described procedure[7b,c] was used for the preparation of benzonorbornadiene.[7a] Distillation of the crude reaction mixture through a 10-in. Vigreux column afforded benzonorbornadiene, bp 72–81° (10 mm) (40% yield) [lit.[7a] bp 82.5–83° (12 mm)]. Spectral properties are in accord with those previously reported.[7c]

Standard Photolysis Procedure.—Approximately 100 ml of 1–2% solution of the substrate was dissolved in reagent grade benzene (unless otherwise specified). The solution was placed in a Pyrex vessel and 5–12 drops (90–216 mg) of acetophenone was added, depending on the amount of substrate. The solution was purged with nitrogen for 15 min prior to, and then throughout, the irradiation. The irradiation was performed in a Rayonnet photochemical reactor equipped with a bank of 16 General Electric F8 T5-BLB lamps (3500 Å). The irradiation was continued overnight or until vinyl absorption was no longer visible in the nmr spectrum.

anti-**9-Acetoxybenznorbornadiene (7).**—The method of Story[8b] was adapted for the preparation of the title compound. From 22 g (0.1 mol) of *tert*-butyl ether **11** was obtained 15 g (75%) of the desired product bp 84–91° (0.15 mm). These physical and spectral properties are in accord with those previously reported for this compound.[10,13]

anti-**9-Benznorbornadienol (12).** A.—The procedure of Tanida,[13] employing methylmagnesium iodide, was applied to the acetate **7**. Recrystallization from hexane gave 70% yield of the alcohol as colorless prisms, mp 104.5–106° (lit. mp 105–106,[13] 104–105° [8a]).

B.—The procedure of Brennan and Battiste[8a] was used. The ether **11**, 21.4 g (0.1 mol), 200 ml of THF, and 100 ml of 50% aqueous H_2SO_4 gave the anti alcohol **12** (13 g, 83%), mp 104.5–106° (lit. mp 105–106,[13] 104–106° [8a]).

exo-**5-Acetoxytetracyclo[5.4.0.0^{2,4}.0^{3,6}]undeca-1(7),8,10-triene (8).**—Treatment of 1.08 g (5.4 mmol) of *anti*-9-acetoxybenzonorbornadiene in 108 ml of hexane with 4 drops of acetophenone, followed by photolysis under the standard photolysis conditions (*vide supra*), gave after solvent removal 1.03 g of crude product. Evaporative distillation (Kugelrohr oven) at 85–90° (0.05 mm) gave 0.91 g (85%) of exo acetate **8** whose purity (>99%) was confirmed by glpc analysis on a 4-ft silicone rubber column. The samples used for the spectral analysis were collected from 4-ft silicone rubber columns (glpc): ir (film) 3.29 (w), 5.78 (s), 8.10 (s), and 13.35 μ (s); nmr (CCl_4) δ 2.12 (m, 4), 2.57 (t, 1, J = 5.0 Hz), 3.24 (m, 1), 3.58 (m, 1), and 4.07 ppm (d, 1, J = 3.5 Hz); mass spectrum (70 eV) *m/e* 200 (molecular ion).

Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.86; H, 6.04.

anti-**9-*tert*-Butoxybenzonorbornadiene (11).**—The procedure of Brennan and Battiste[8a] was used for the preparation of the title compound. Benzonorbornadiene (142 g, 1.0 mol), benzene (360 ml), cuprous bromide (300 mg), and *tert*-butyl perbenzoate (76 g, 0.39 mol) afforded after two distillations 26 g (32%) of *tert*-butyl ether **11**, bp 72–80° (0.2 mm). Pure *tert*-butyl ether was obtained upon redistillation through a 24-in. stainless steel spinning-band column, bp 78–80° (0.23 mm). Recrystallization from hexane gave colorless crystals, mp 48–49° (lit.[8a] mp 48–49°). The spectral characteristics of **11** are identical with those previously reported.[8a]

endo-**5-Acetoxytetracyclo[5.4.0.0^{2,4}.0^{3,6}]undeca-1(7),8,10-triene (10).**—Treatment of 3.1 g (15.5 mmol) syn acetate **9** in 400 ml of hexane with 20 drops of acetophenone, followed by photolysis under the standard conditions, gave after solvent removal and evaporative distillation at 90° (0.04 mm) 2.93 g (95%) of clear, pure (glpc analysis, 4-ft silicone rubber column) liquid: ir (film) 3.25 (w), 5.77 (s), 8.07 (s,), and 13.30 μ (s); nmr (CCl_4) δ 1.40 (s, 3), 2.35 (m, 1), 2.64 (t, 1, J = 5.0 Hz), 3.07 (m, 1), 3.93 (m, 1), 5.19 (q, 1, J = 7.5 Hz), 6.93–7.52 (m, 4); mass spectrum (70 eV) *m/e* 200 (molecular ion).

Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.90; H, 5.84.

exo-**Tetracyclo[5.4.0.0^{2,4}.0^{3,6}]undeca-1(7),8,10-trien-5-ol (13).** A.—To a stirred suspension of 2.0 g (52.5 mmol) of lithium aluminum hydride in 50 ml of anhydrous ether was added slowly, over a 20-min period, a solution of 6.7 (33.5 mmol) of *exo*-acetate **8** in 50 ml of anhydrous ether. The reaction mixture was stirred for an additional 45 min and the excess lithium aluminium hydride was decomposed by the careful (dropwise) addition of water. The resulting salts were removed by filtration. The solvent was removed at reduced pressure and the crude product was distilled at 94–95° (0.03 mm) in a Kugelrohr oven. There was obtained 4.2 g (80%) of a clear viscous oil which crystallized upon standing: mp 61.5–63.7°; ir (film) 3.0 (s), 9.32 (m), 13.45 μ (s); nmr (CCl_4) δ 1.89 (m, 1), 2.45 (t, 1, J = 6.0 Hz) 3.08 (m, 1), 3.53 (m, 2), 5.00 (s, 1), 6.83–7.50 ppm (m, 4).

B.—Treatment of 1.0 g (6.3 mmol) of *anti*-9-benzonorbornadienol (**12**) in 100 ml of benzene with 5 drops of acetophenone under the standard photolysis conditions gave 0.76 g of exo alcohol **13** (76%) as a white solid (mp 61.5–63.5°) after evoporative distillation in a Kugelrohr oven at 90° (0.04 mm). The exo-alcohol **13** prepared in this manner is identical in physical and spectral properties with that described above (A).

The exo alcohol **13** (0.90 g, 5.7 mmol) was converted into the corresponding *p*-nitrobenzoate **16** using 4 ml of pyridine and 1.13 g (6.1 mmol) of *p*-nitrobenzoyl chloride.[14] The *p*-nitrobenzoate was obtained as yellow crystals (1.00 g, 65%): mp 88–89°; ir (Nujol mull) 5.83 (s), 6.53 (s), 7.80 (s), 14.0 μ (s); nmr ($CDCl_3$)

(12) (a) R. J. Piccolini and S. Winstein, *Tetrahedron Lett.*, No. 13, 4 (1959); (b) R. J. Piccolini, Ph.D. Dissertation, UCLA, Los Angeles, Calif., 1960.

(13) H. Tanida, and T. Tsuji, *J. Org. Chem.*, **29**, 849 (1964).

(14) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 736.

δ 2.24 (m, 1), 2.67 (t, 1, J = 5.0 Hz), 3.44 (m, 1), 3.69 (m, 1), 4.38 (d, 1, J = 4.0 Hz), 7.05–7.60 (m, 4), 8.20 ppm (s, 4).

Anal. Calcd for $C_{18}H_{13}NO_4$: C, 70.36; H, 4.23; N, 4.56. Found: C, 70.67; H, 4.08; N, 4.38.

syn-9-**Chlorobenzonorbornadiene** (14).—To a stirred solution of 1.90 g (12.0 mmol) of exo alcohol 13 in 20 ml of anhydrous ether was added slowly by syringe 1.44 g (12.0 mmol) of thionyl chloride in 2.5 ml of anhydrous ether over a 5-min period. The reaction mixture was stirred overnight at room temperature. The reaction mixture was then washed successively with cold water and saturated $NaHCO_3$ solution and then dried ($MgSO_4$). The solution was then filtered and the solvent was removed at reduced pressure, to leave a yellow liquid which was evaporatively distilled in a Kugelrohr oven at 80–85° (0.05 mm) to afford a white solid (1.71 g, 82%), whose physical and spectral properties are in accord with those reported by Cristol and Nachtigall.[9,10]

exo-5-*tert*-**Butoxytetracyclo[5.4.0.0^{2,4}.0^{3,6}]undeca-1(7),8,10-triene** (15).—Treatment of 1.1 g (5.14 mmol) of *anti*-9-*tert*-butoxybenzonorbornadiene in 100 ml of benzene with 5 drops of acetophenone under the standard photolysis conditions gave, after evaporative distillation in a Kugelrohr oven, 0.87 g (79%) of 15 as a viscous liquid which solidified on cooling. Recrystallization from hexane gave an analytical sample: mp 71–72°; ir (Nujol mull) 8.36 (m), 9.27 (s), 13.35 μ (s); nmr ($CDCl_3$) δ 1.21 (s, 9), 1.85 (m, 1), 2.50 (m, 1), 3.13 (m, 1), 3.37 (d, 1, J = 7.6 Hz), 3.63 (m, 1), 6.90–7.60 (m, 4).

Anal. Calcd for $C_{15}H_{18}O$: C, 84.11; H, 8.41. Found: C, 84.04; H, 8.69.

syn-9-**Acetoxybenzonorbornadiene** (9).—The exo *tert*-butyl ether 15 (4.3 g, 20.0 mmol) was dissolved in 32 ml of glacial acetic acid containing 5.9 ml of acetic anhydride. The solution was cooled to a temperature just above its freezing point and was then added rapidly, with vigorous swirling, to a flask containing 4.1 g of 70% perchloric acid at 0°. The reaction flask was swirled in an ice bath for 4 min, then poured into 200 ml of a 1:1 ice–water mixture and extracted with chloroform. The chloroform solution was washed with a saturated $NaHCO_3$ solution and dried over anhydrous K_2CO_3. The solution was filtered and the solvent was removed at reduced pressure. The resulting pale yellow liquid was distilled [74–76° (0.04 mm)] in a Kugelrohr oven to give 3.2 g (81%) of syn acetate 9: ir (film) 5.74 (s), 8.08 (s), 9.55 (s), 13.51 (s), 14.36 μ (s); nmr (CCl_4) δ 1.55 (s, 3), 3.80 (q, 4, J = 5.0 Hz, J = 2.0 Hz), 4.83 (t, 1, J = 2.4 Hz), 6.60 (t, 2, J = 2.4 Hz), 6.77–7.28 (A_2B_2, 4).

The product obtained (*i.e.*, 9) exhibits physical and spectral properties identical with those reported by Cristol and Nachtigall.[10]

syn-9-**Hydroxybenzonorbornadiene** (17).—To a stirred solution of 0.59 g (15.5 mmol) of lithium aluminum hydride in 25 ml of anhydrous ether was added slowly, over a 2-hr period, a solution of 3.13 g (15.6 mmol) of *syn*-9-acetoxybenzonorbornadiene (9) in 25 ml of anhydrous ether. The reaction was stirred for an additional 30 min. The excess lithium aluminum hydride was decomposed by the dropwise addition of water and the salts were removed by filtration. The solvent was distilled at reduced pressure, leaving 2.14 g (84%) of a clear viscous liquid which solidified on standing to give, upon recrystallization from hexane: white needles; mp 89–92.5°; ir (film) 2.92 (m), 9.35 (s), 13.68 (s), 14.43 μ (s); nmr (CCl_4) δ 3.17 (s, 1), 3.58 (q, 2, J = 5.0 Hz, J = 2.0 Hz), 4.08 (t, 1, J = 2.0 Hz), 6.60 (t, 2, J = 2.0 Hz), 6.90–7.42 ppm (A_2B_2, 4).[15]

endo-**Tetracyclo[5.4.0.0^{2,4}.0^{3,6}]undeca-1(7),8,10-trien-5-ol** (18).

A.—To a solution of 0.10 g (7.2 mmol) of lithium aluminum hydride in 10 ml of anhydrous ether at 0° was added dropwise a solution of 0.5 g (2.5 mmol) of endo acetate 10 in 5 ml of anhydrous ether over a 15-min period. After the mixture was stirred for an additional 10 min, the excess lithium aluminum hydride was decomposed by the dropwise addition of water. The solution was filtered, dried (K_2CO_3), and filtered again, and the solvent was removed under reduced pressure. Evaporative distillation of the residue in a Kugelrohr oven at 83° (0.06 mm) afforded 0.29 g (76%) of endo alcohol 18 as a viscous oil: ir (film) 2.90 (m), 9.17 (s), 13.2 μ (s); nmr (CCl_4) δ 1.20 (s, 1), 2.23 (m, 2), 2.73 (m, 1), 4.16 (m, 1), and 7.08 ppm (m, 4).[15]

B.—Treatment of 1.08 g (6.8 mmol) of syn alcohol 17 in 100 ml of benzene with 6 drops of acetophenone under the standard photolysis conditions gave, after evaporative distillation in a Kugelrohr oven at 71° (0.07 mm), 0.75 g (75%) of endo alcohol 18. On some occasions we have found the endo alcohol to undergo substantial isomerization to its syn isomer 17 upon distillation. Therefore, we ordinarily used the crude endo alcohol without purification for the further chemical transformations.

endo-**Tetracyclo[5.4.0.0^{2,4}.0^{3,6}]undeca-1(7),8,10-trien-5-ol** *p*-**Nitrobenzoate** (19).—The endo alcohol 18 (0.10 g, 0.63 mmol) was dissolved in 2 ml of carbon tetrachloride containing 0.05 ml of dry pyridine and cooled to 0° in an ice bath. *p*-Nitrobenzoyl chloride (0.11 g, 0.59 mmol) was added to the solution in one portion and the reaction vessel was immediately stoppered and placed in the refrigerator overnight. The white crystals which had formed were removed by filtration and the solvent was distilled at reduced pressure to give a yellow oil which solidified. Recrystallization from hexane gave 0.09 g (44%) of yellow needles: mp 166–168° dec; ir (Nujol mull) 5.82 (s), 6.57 (s), 7.88 (s), 13.39 (s), 13.90 μ (s); nmr (CCl_4) δ 2.33–2.72 (m, 2), 3.05 (m, 1), 3.95 (m, 1), 5.47 (q, 1, J = 7.0 Hz, J = 3.2 Hz), 6.75–8.20 ppm (m, 8).

Anal. Calcd for $C_{18}H_{13}NO_4$: C, 70.36; H, 4.23. Found: C, 70.50; H, 4.22.

Hydrogen-Bonding Studies.[12]—The hydrogen-bonding studies were restricted to the first overtone region for hydroxyl stretching in the near-infrared (15600–13900 Å) using a Cary Model 14 automatic recording spectrophotometer at the following settings: speed, 5 Å sec^{-1}; chart, 5 in. min^{-1}; slit control, 20. Matched 1-cm, 5-cm, and 10-cm quartz cells were used. Carbon tetrachloride was used as solvent. Concentrations of substrates varied from 10^{-1} to 10^{-3} M in all cases.

The areas of the absorption peaks (B values) were determined by multiplying the extinction coefficients of the bands by their bandwidth at half-height (in reciprocal centrimeters). These values are tabulated in Table I (*cf.* text).

Registry No.—**8,** 29577-56-8; **10,** 29641-80-3; **13,** 29577-57-9; **15,** 29577-58-0; **16,** 29641-81-4; **17,** 23526-79-6; **18,** 29577-60-4; **19,** 29577-61-5.

(15) This compound was not subjected to carbon–hydrogen combustion analysis since it decomposed upon standing.

The Synthesis and Some Conformational Observations on the 3,10-Diazabicyclo[4.3.1]decane System

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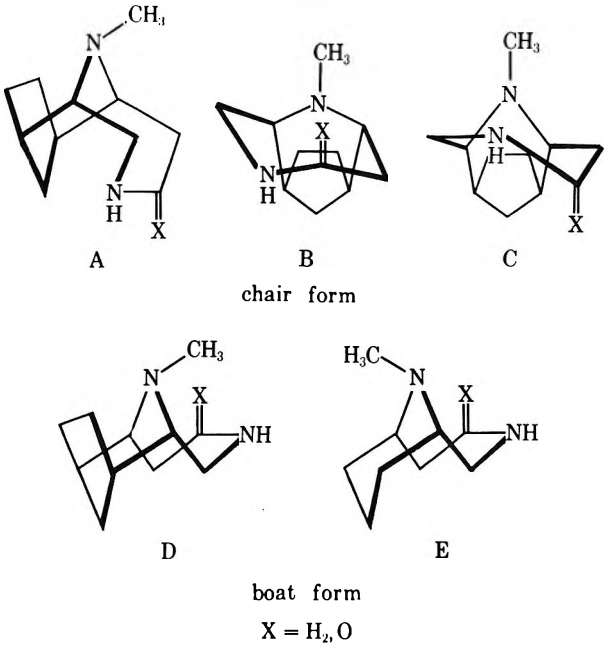
10-Methyl-3,10-diazabicyclo[4.3.1]decane (**7**) and its 7,9-*exo*-ethano derivative **12** were prepared by $LiAlH_4$ reduction of 10-methyl-3,10-diazabicyclo[4.3.1]decan-4-one (**3**) and its 7,9-*exo*-ethano derivative **9**, both of which were obtained by the Schmidt reaction of pseudopelletierine (**1**) and 6,8-*exo*-ethanopseudopelletierine (**8**), respectively. The same reduction of **3** afforded a stable aluminum complex, tris(10-methyl-3,10-diazabicyclo-[4.3.1]decane)aluminum hydroxide (**6**) in 76% yield, but reduction of **9** yielded no such stable complex. Treatment of **7** with 1 equiv of methylene iodide gave 10-methyl-3,10-diazatricyclo[4.3.1.1^{3,10}]undecanium iodide (**19**).

Recently we reported the synthesis of 9-methyl-9-azatricyclo[3.3.1.0^{3,7}]nonane (9-methyl-9-azanoradamantane) from pseudopelletierine (**1**) (9-methyl-9-azabicyclo[3.3.1]nonan-3-one) by the transannular C–H insertion reaction of the corresponding 3-carbene.[1] As an extension of a study on the azabicyclic and azatricyclic systems, this paper deals with the syntheses of the amines **7** and **12** from **1** and 6,8-*exo*-ethanopseudopelletierine (**8**),[2,3] respectively, and the chemical behavior and nmr spectra of these compounds and the 4-ones (**3** and **9**).

Chart I



Results and Discussion

The Schmidt reaction of pseudopelletierine (**1**) proceeded smoothly to give 10-methyl-3,10-diazabicyclo-[4.3.1]decan-4-one (**3**) in high yield as reported by Paquette and Wise.[4] The Beckmann rearrangement of **1** oxime hydrochloride (**2**) with polyphosphate ester in refluxing chloroform afforded a complex mixture of unidentifiable products together with a trace of **3**. **3** gave a methiodide **4** and hydrochlorides **5a** + **5b** by routine procedures (Scheme I).

The Schmidt reaction of **8** similarly gave a lactam **9**[3] (93%). The structure was evidenced by analytical and spectral data; the nmr signal due to a C_2 equatorial proton at τ 6.20 (double d, J = 14.8 and 3.7 Hz) is similar to that of **3**, indicating a similar conformation of **9** to that of **3** as shown in Chart I. **9** gave a hydrochloride **11**, while **9** did not react with methyl iodide even on heating at 90° in a sealed tube in contrast with the facile formation of **4** from **3** and methyl iodide. Such a behavior of **9** is quite similar to that of **8** (see Scheme II); the lone electron pair on nitrogen is sterically hindered by the proximity of the exo ethano bridge. Hence, for **9** was assigned an anti orientation of the 10-methyl group against the 7,9-ethano bridge.

Reduction of the cyclic lactam **3** with lithium aluminum hydride in refluxing tetrahydrofuran afforded a crystalline aluminum complex **6** in 76% yield, which was characterized as tris(10-methyl-3,10-diazabicyclo-[4.3.1]decane)aluminum hydroxide on the basis of analytical and nmr data (Figure 1, **6**); the nmr signals due to three *N*-methyl protons appear in a sharp singlet at τ 7.33, indicating that **6** has a symmetrical cis form with a C_3 symmetry of the octahedral structure. Furthermore, a broad doublet (J = 9.0 Hz) at τ 8.83 was assignable to a C_8 endo proton, supporting a boat conformation of the homopiperazine ring and a chair conformation of the piperidine ring in **6**.[5] The complex **6** was very stable to alkali; treatment with 30% aqueous sodium hydroxide liberated only a trace of a free amine **7**. However, **6** afforded **7** readily by basifying the solution in hydrochloric acid.

The amine **7** was characterized as 10-methyl-3,10-diazabicyclo[4.3.1]decane on the basis of analytical, spectral, and chemical evidence; the mass spectrum had a M^+ at m/e 154 ($C_9H_{18}N_2$) and the nmr spectrum (Figure 1, **7**) had signals at τ 6.70–7.20 (m, 6, $2NCH_2$ and 2NCH), 7.38 (s, 3, NCH_3), 7.50–8.90 (m, 8, $4CH_2$), and 8.06 (s, 1, NH, disappeared on deuteration). **7** gave a dipicrate, mp 238–240°, and a hydriodide **14** of the methiodide **15** (Scheme III).

(1) (a) T. Sasaki, S. Eguchi, and T. Kiriyama, *J. Amer. Chem. Soc.*, **91**, 212 (1969); (b) T. Sasaki, S. Eguchi, and T. Kiriyama, *Tetrahedron*, **27**, 893 (1971).

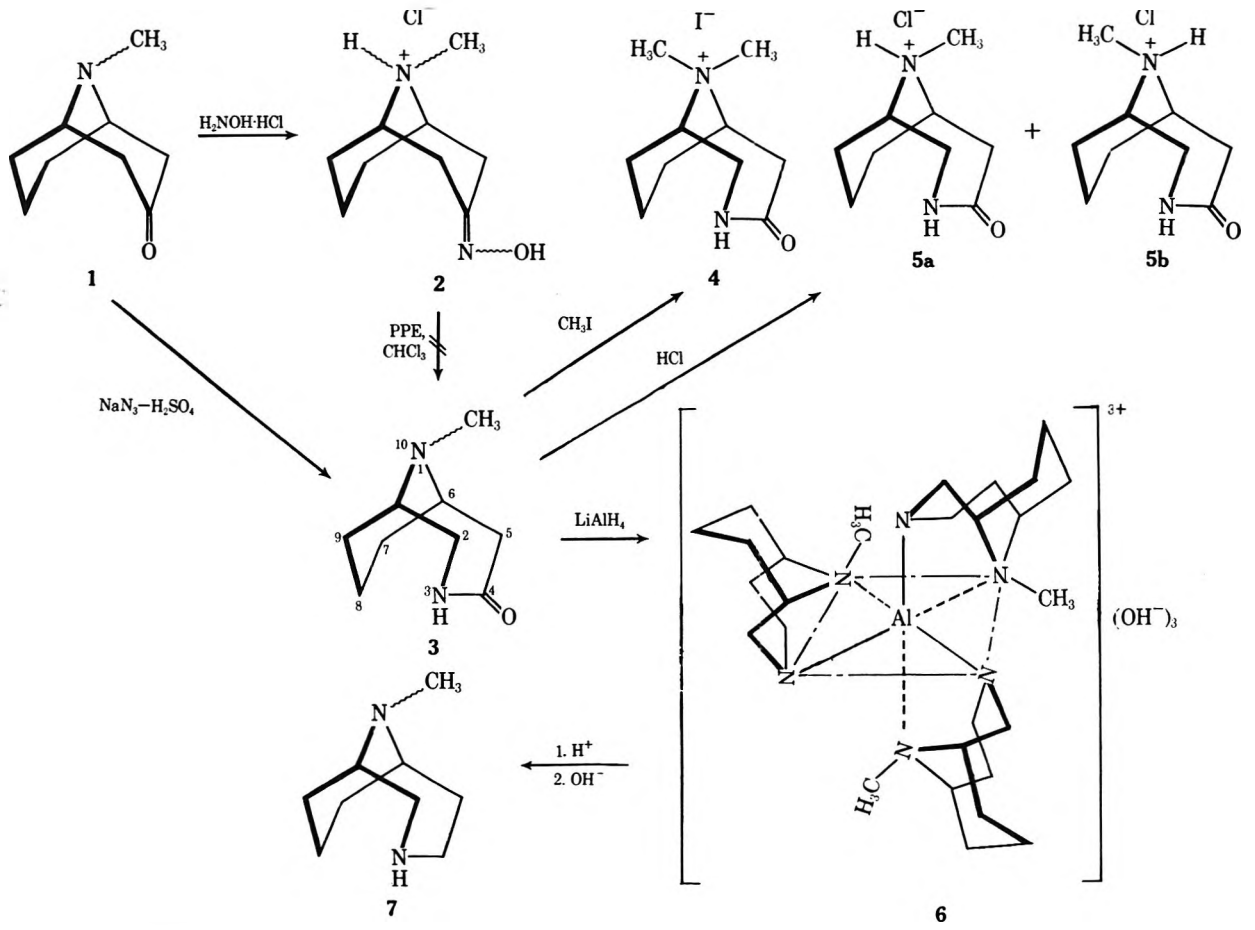
(2) L. A. Paquette and J. W. Heimaster, *J. Amer. Chem. Soc.*, **88**, 763 (1966).

(3) The ethano-bridged **8** and **9** could be named as 10-methyl-10-azatricyclo[4.3.1.1^{5,6}]undecan-3-one and 11-methyl-3,11-diazatricyclo[4.4.1.1^{7,10}]-dodecan-4-one, respectively. However, we prefer the above trivial name since the nomenclature as the tricyclic compounds can not distinguish two possible configurational isomers corresponding to the *exo*- and *endo*-ethano derivatives: *cf.* G. Ferguson, W. D. K. Macrossan, J. Martin, and W. Parker, *J. Chem. Soc. B*, 242 (1968).

(4) (a) L. A. Paquette and L. Wise, *J. Amer. Chem. Soc.*, **87**, 1561 (1965). (b) For mass spectrum of **3**, see A. M. Duffield, C. Djerassi, L. Wise, and L. A. Paquette, *J. Org. Chem.*, **31**, 1599 (1966).

(5) Appearance of this proton at such a characteristically higher field could be explained by anisotropy of the C_1–C_2 and C_6–C_8 bonds: *cf.* R. G. Foster and M. C. McIvon, *Chem. Commun.*, 280 (1967).

SCHEME I



The lithium aluminum hydride reduction of **9** gave the corresponding amine **12** as a colorless crystal. The structure was evidenced by analytical and spectral data; the nmr spectrum had signals at τ 6.68–7.25 (m, 6, $2NCH_2$ and 2NCH), 7.37 (s, 3, NCH_3), 7.46–8.30 (m, 5, C_7 H, C_9 H, 2 C_5 H, and C_8 endo H), 8.15 (s, 1, NH, disappeared on deuteration), 8.50 (broad s, 4, 7,9-ethano bridge), and 8.93 (broad double t, J = 12.5 and 6.0 Hz, 1, C_8 exo H).

The fact that no stable aluminum complex was produced in the reduction of **9** in contrast with **3** could be explained by an anti orientation of the NCH_3 to the 7,9-ethano bridge in **9**, since in this configuration **12** can not be inverted to a boat form of the homopiperazine ring, an indispensable form to produce a stable aluminum complex like **6**.

As summarized in Scheme IV, **12** did not afford a dimethiodide but a monomethyl hydriodide **21** with excess methyl iodide.

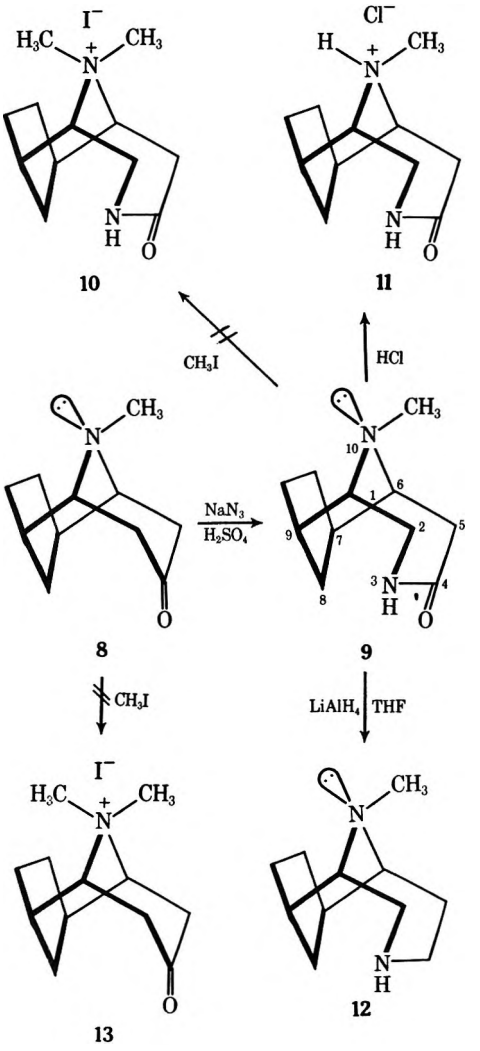
Both **7** and **12** gave the corresponding dihydrochlorides **16** and **20** with excess hydrogen chloride. However, the behavior of **7** on treatment with 1 equiv of trifluoroacetic acid was quite different from that of **12** as shown by the nmr spectra; the nmr spectrum of **7** in the presence of 1 equiv of trifluoroacetic acid had a characteristic signal at τ 8.93 in a broad doublet (J = 9.3 Hz) assignable to a C_8 endo proton of the monocation **17** with a chair–boat conformation (Figure 1, **17** and Scheme III). The whole spectral pattern of **17** was also very similar to that of **6**, supporting above assignment. Contrarily, the nmr spectrum of **12** in the presence of 1 equiv of trifluoroacetic acid had signals corresponding to just intermediate ones between the free base **12** and the dication **20**, indicating that the monocation of **12** could be interpreted as an equilibrating mixture of **22** and **23** on the nmr time scale. This fact indicates that the inversion of the homopiperazine ring in **12** is impossible because of the severe steric hindrance of the anti NCH_3 group.

The formation of a stable aluminum complex **6** and a stable monocation **17** from **7** led to the examination of a reaction of **7** with methylene iodide. Treatment of **7** with 1 equiv of methylene iodide at room temperature afforded a 3,10-methano derivative **18** which liberated easily hydrogen iodide to give 10-methyl-3,10-diazatricyclo[4.3.1.$1^{3,10}$]undecanium iodide (**19**) as a colorless crystal. The structure was determined on the basis of analytical and spectral data; in the nmr spectrum (Figure 1, **19**), appearance of a characteristic broad doublet at τ 8.83 (J = 10.2 Hz) assignable to a C_8 endo proton supported the assigned structure.

Evidently both **7** and **16** take a chair–chair conformation on the basis of the different nmr spectra from those of **6**, **17**, and **19**, all of which were concluded to take a chair–boat conformation as discussed above. A chair–chair conformation is also assignable for **12** as well as **20** and **21** by their nmr spectral patterns similar to those of **7**, **15**, and **16**. In the series of **12**, the chair–chair conformation is apparently favored because of a severe steric hindrance in a chair–boat form due to the presence of an anti *N*-methyl group.

In a *N*-methyl homopiperazine ring, there are three possible chair conformers, A, B, and C, as depicted in Chart I. An inspection of the Dreiding stereomodel

Scheme II



suggested that the B and C forms suffer from a considerable internal strain due to the bond angle deformation at C_1 and C_6, which is lacking in A form. Hence, A is the most plausible form as a chair–chair conformer of **7** and **12**. Furthermore, the lactams **3** and **9** had amide bands at 1648 and 1650 cm^{-1}, respectively, which correspond to the normally conjugated amide bands. Thus, the A form is also the most plausible for **3** and **9**, since a considerable distortion of the C_2–N_3–C_4–C_5 plane is anticipated in B and C forms, where the normal lactam character could not be expected.

Finally, a nitrogen pyramidal inversion problem is mentioned briefly on the basis of the nmr data of the hydrochlorides. The hydrochloride of **3** revealed two sharp singlets at τ 6.81 and 6.89 in *ca.* 1:2 ratio, which were assignable to *N*-methyl protons of **5a** and **5b** (Scheme I), while the hydrochloride of **9** exhibited only one singlet at τ 7.00 due to *N*-methyl protons of **11** (Scheme II). Although the nitrogen pyramidal inversion is known to require relatively small activation energy, the protonation to an amine function requires much less energy.[6] Hence, the above facts indicate the presence of the *N*-pyramidal inversion in **3** but not in **9** (at room temperature). The hydrochloride **16** exhibited only one singlet at τ 6.94 due to *N*-methyl protons (Figure 1, **16**); this could be reasonably explained by the protonation *via* a monocation like **17** rather than by the absence of the *N*-pyramidal inversion. All of these results are in good agreement with the chemical behaviors described above.

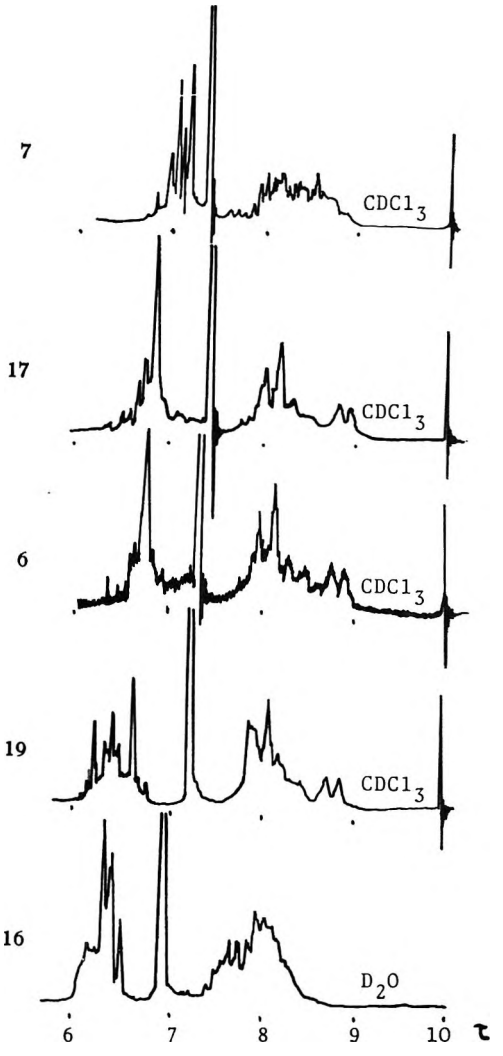


Figure 1.—The 60-MHz spectra of **7**, **17**, **6**, **19**, and **16**. All compounds except **6** were deuterated by shaking in D_2O. For **16**, $CHCl_3$ was used as an internal reference.

Experimental Section[7]

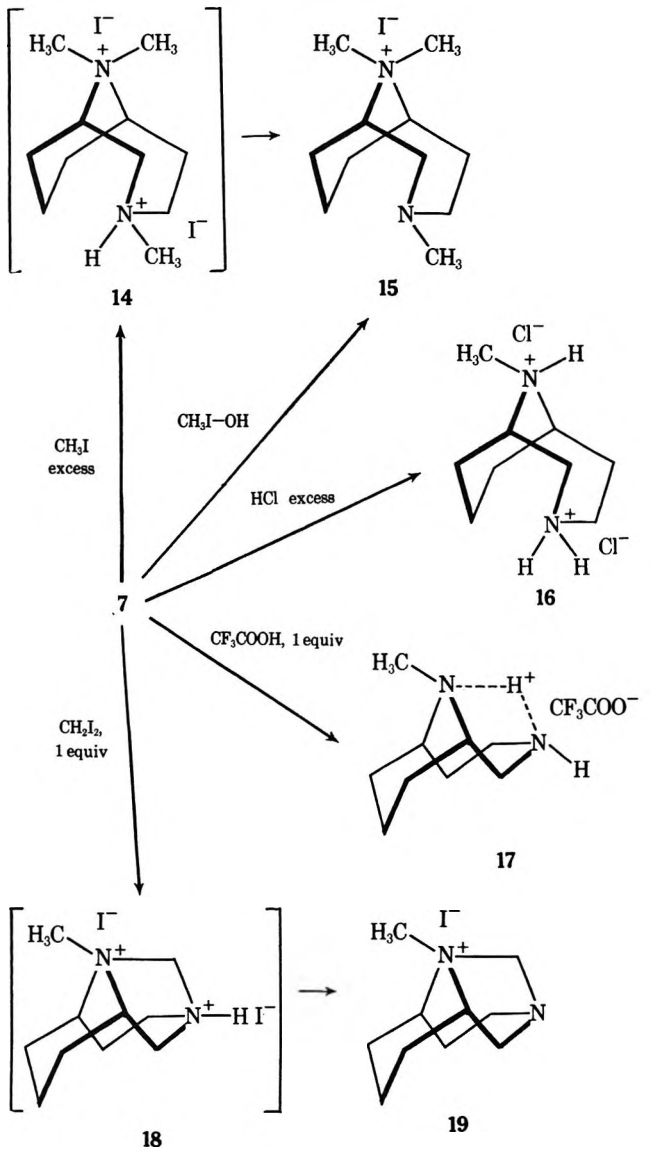
10-Methyl-3,10-diazabicyclo[4.3.1]decan-4-one (3).—This was prepared by the reported procedure:[4a] mp 164–166° (lit.[4a] mp 164–166°); ir (KBr) 3160, 3040, 2880, and 1648 cm^{-1}; nmr ($CDCl_3$) τ 2.56 (broad s, 1, NH, disappeared on deuteration), 6.11 (d d, 1, J = 15.0 and 4.1 Hz, C_2 eq H), 6.73–7.36 (m, 3, C_2 ax H, C_1 H, and C_6 H), 7.48 (s, 3, NCH_3), and 7.50–8.72 (m, 8, remaining protons).

7,9-*exo*-Ethano-10-methyl-3,10-diazabicyclo[4.3.1]decan-4-one (9).[3]—The Schmidt reaction of 6,8-*exo*-ethanopseudopelletierine (**8**)[2] was carried out similarly to the preparation of **3** by using 8.95 g (50 mmol) of **8**, 20 ml of concentrated sulfuric acid, and 6.5 g (100 mmol) of sodium azide to give 8.98 g (93%) of **9**. An analytical sample was obtained by recrystallization from *n*-hexane–ethyl acetate as colorless needles: mp 154°; ir (KBr) 3240, 3160, 3020, 2925, and 1650 cm^{-1}; nmr ($CDCl_3$) τ 3.50

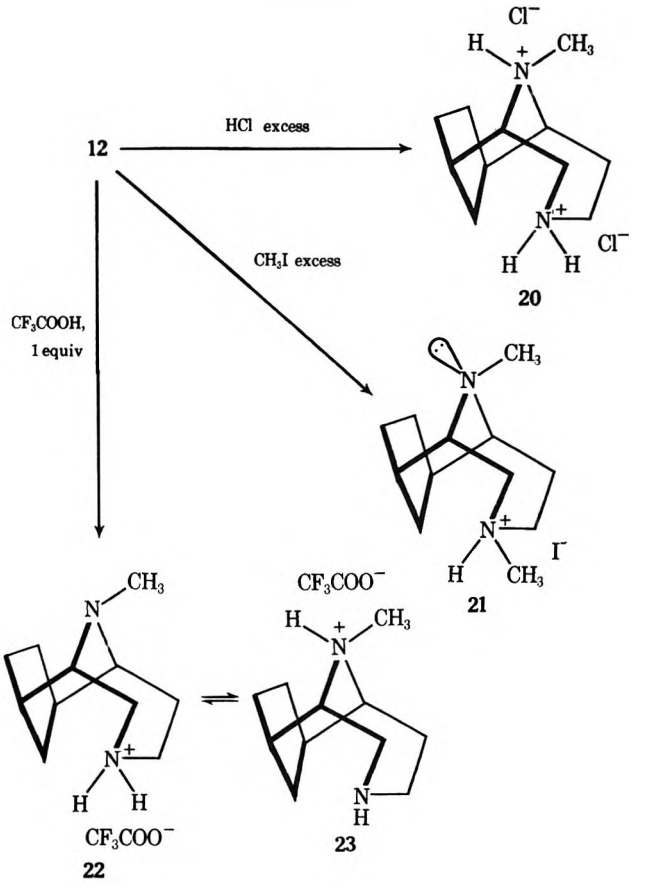
(6) (a) J. B. Lambert, R. G. Keske, R. E. Carhart, and A. P. Jovanovich, *J. Amer. Chem. Soc.*, **89**, 3761 (1967). (b) For a review on the pyramidal inversion, see A. Rauk, L. C. Allen, and K. Mislow, *Angew. Chem.*, **82**, 453 (1970).

(7) All melting points were obtained on a hot-stage type micromelting point apparatus and are uncorrected. Nmr spectra were recorded on a JEOL JNM-C-60HL spectrometer at 60 MHz and mass spectra on a JEOL JMS-01SG mass spectrometer at 75 eV. Ir spectra were obtained with a JASCO IR-S ir spectrophotometer. Microanalyses were carried out with a Perkin-Elmer 240 elemental analyzer.

SCHEME III



SCHEME IV



(broad s, 1, NH, disappeared on deuteration), 6.20 (d d, 1, J = 14.8 and 3.9 Hz, C_2 eq H), 6.55–7.09 (m, 3, C_2 ax H, C_1 H, and C_6 H), 7.10–7.48 (m, 2, C_5 CH_2), 7.51 (s, 3, NCH_3), 7.62–7.94 (m, 2, C_7 H and C_9 H), 8.08–8.68 (m, 5, 7,9-ethano bridge and C_8 endo H), and 8.96 (d, t, 1, J = 12 and 4.0 Hz, C_8 exo H); mass spectrum m/e 194 (M^+), 136, 122, 108, 95, and 94.

Anal. Calcd for $C_{11}H_{18}ON_2$: C, 74.11; H, 10.18; N, 15.71. Found: C, 74.15; H, 10.10; N, 15.74.

10-Methyl-3,10-diazabicyclo[4.3.1]decan-4-one Methiodide (4).—To a solution of 0.17 g (1.0 mmol) of **3** in 5 ml of ethanol was added dropwise 0.50 g (3.5 mmol) of methyl iodide, resulting in a rapid precipitation of colorless crystals, which were filtered and washed with ethanol to give **4**: mp >300°; ir (KBr) 3240, 2928, 2880, 1664, 1455, and 1360 cm^{-1}.

Anal. Calcd for $C_{10}H_{19}ON_2I$: C, 38.72; H, 6.17; N, 9.03. Found: C, 38.82; H, 5.90; N, 9.10.

10-Methyl-3,10-diazabicyclo[4.3.1]decan-4-one Hydrochloride (5a and 5b).—Into a solution of 0.17 g (1.0 mmol) of **3** in 10 ml of dry benzene was bubbled dry hydrogen chloride gas. The resulting colorless precipitates were recrystallized from ethanol to give hygroscopic needles of **5a** and **5b**: mp 229–233°; ir (KBr) 3160, 3020, 2930–2420, 1695, 1629, and 1446 cm^{-1}; nmr (D_2O) τ 5.60–6.70 (m, 5, C_2 CH_2, C_1 H, C_6 H, and C_5 H), 6.81 and 6.89 (each s, total 3, NCH_3), and 7.00–8.50 (m, 7, other protons).

Anal. Calcd for $C_9H_{17}ON_2Cl$: C, 52.81; H, 8.37; N, 13.69. Found: C, 52.63; H, 8.70; N, 13.55.

Hydrochloride 11 of 9.—This was prepared similarly as above as a very hygroscopic crystal: mp 247–249°; ir (KBr) 3200, 2930–2650, 1640, and 1482 cm^{-1}; nmr (D_2O) τ 5.84–6.84 (m, 5, C_2 CH_2, C_1 H, C_6 H, and one of C_5 CH_2), 7.00 (s, 3, NCH_3), 7.17–7.64 (m, 3, C_7 H, C_9 H, and one of C_5 CH_2), 7.64–8.42 (m, 5, 7,9-ethano bridge and C_8 endo H), and 8.73 (d t, 1, J = 12 and 4 Hz, C_8 exo H).

Anal. Calcd for $C_{11}H_{19}ON_2Cl$: C, 57.26; H, 8.30; N, 12.14. Found: C, 57.38; H, 8.44; N, 11.88.

Tris(10-methyl-3,10-diazabicyclo[4.3.1]decane)aluminum Hydroxide (6).—A mixture of 8.4 g (50 mmol) of **3** and 1.9 g (50 mmol) of lithium aluminum hydride in 100 ml of dry tetrahydrofuran was refluxed for 1 day. After cooling, the unreacted reducing agent was decomposed by adding aqueous tetrahydrofuran under ice cooling. The mixture was diluted with 500 ml of water and extracted with methylene chloride (six 50-ml portions) after addition of 50 ml of 30% aqueous sodium hydroxide. The combined extracts were dried (Na_2SO_4) and removal of the solvent afforded 7.0 g (76%) of **6** as colorless needles. An analytical sample was obtained after recrystallization from ethyl acetate: mp 180°; ir (KBr) 2620–3000, 1548, 1437, and 1153 cm^{-1}; nmr ($CDCl_3$), see Figure 1, **6**.

Anal. Calcd for $C_{27}H_{51}N_6Al(OH)_3 \cdot {}^1/_2H_2O$: C, 59.31; H, 10.14; N, 15.37. Found: C, 59.35; H, 10.22; N, 15.54.

10-Methyl-3,10-diazabicyclo[4.3.1]decane (7).—A solution of 6.5 g (0.12 mol) of **6** in 50 ml of water was acidified with 20 ml of concentrated hydrochloric acid and was heated at 90° for 10 min. The cooled solution was basified with 20% aqueous sodium hydroxide and extracted with methylene chloride (six 50-ml portions). The combined extracts were dried (Na_2SO_4) and the solvent was removed to give 5.4 g (90%) of crude **7** as a syrupy oil. An analytical sample was obtained by dry distillation under reduced pressure as a hygroscopic and sublimable solid: mp 43–46° (sealed tube); ir (KBr) 3280, 2925, and 1442 cm^{-1}; mass spectrum m/e 154 (M^+); nmr, see Figure 1, **7**.

A picrate of **7** had mp 238–240° and 253–255° dec.

Anal. Calcd for $C_{21}H_{24}O_{14}N_8$: C, 43.45; H, 4.17; N, 19.30. Found: C, 43.77; H, 3.96; N, 19.18.

7,9-*exo*-Ethano-10-methyl-3,10-diazabicyclo[4.3.1]decane (12).[3]—The lithium aluminum hydride reduction of 7.75 g (40 mmol) of **9** under the similar conditions as described on **6** and work-up gave 5.47 g (76%) of **12** as a syrupy oil, which was purified by dry distillation under reduced pressure to give **12** as a hygroscopic

and sublimable crystal: mp 66–69° (sealed tube); ir (KBr) 3360, 2860, and 1450 cm^{-1}; mass spectrum *m/e* 180 (M^+).

Anal. Calcd for $C_{23}H_{26}O_{14}N_8$: C, 45.55; H, 4.32; N, 18.48. Found: C, 45.56; H, 4.41; N, 18.39.

The hydrochloride **20** of **12** was very hydroscopic and dissolved directly in D_2O for nmr measurement: nmr τ 5.82–6.60 (m, 6, $2NCH_2$, C_1 H, and C_6 H), 6.84 (s, 3, NCH_3), and 7.10–8.71 (m, 10, other protons).

The monotrifluoroacetic acid salt (**22** and **23**) of **12** was prepared in benzene solution and after removal of the solvent, the remained mono salt was dissolved in D_2O for nmr: nmr τ 6.40–6.93 (m, 4, $2NCH_2$), 6.93–7.22 (m, 2, C_1 H and C_6 H), 7.28 (s, 3, NCH_3), 7.44–8.27 (m, 5, C_5 CH_2, C_7 H, C_9 H, and C_8 endo H), 8.39 (broad s, 4, 7,9-ethano bridge), and 8.78 (d, t, 1, J = 12 and 3.7 Hz, C_8 exo H).

10-Methyl-3,10-diazatricyclo[4.3.1.$1^{3,10}$]undecanium Iodide (19).—To a solution of 0.072 g (0.50 mmol) of **7** in 5 ml of dry benzene was added a solution of 0.134 g (0.50 mmol) of methylene iodide in 5 ml of dry benzene with stirring at room temperature. Stirring was continued for 1 hr. Removal of the solvent under reduced pressure left a brownish residue which was dissolved in ethanol and treated with Norit A to afford 0.023 g of **19** as a colorless prism: mp 182–185°; ir (KBr) 3180–2800, 1540, 1472, and 1440 cm^{-1}; nmr, see Figure 1, **19**.

Anal. Calcd for $C_{10}H_{19}N_2I$: C, 40.83; H, 6.51; N, 9.52. Found: C, 40.85; H, 6.54; N, 9.74.

3,10,10-Trimethyl-3,10-diazabicyclo[4.3.1]decanium Iodide (15).—A mixture of 0.15 g (1.0 mmol) of **7** and 0.43 g (3.0 mmol) of methyl iodide in 10 ml of dry benzene was stirred at room temperature for 30 min. Removal of the solvent and surplus methyl iodide under reduced pressure gave a hydriodide (**14**) of **15**, which on treatment with Norit A in ethanol afforded 0.12 g (38%) of **15** as prisms: mp 268–270°; ir (KBr) 3000, 2920, 2870, 1500, 1440, and 1134 cm^{-1}; nmr ($CDCl_3$) τ 5.98–6.33 (m, 4, C_1 H, C_6 H, and C_2 CH_2), 6.48 (s, 6, $N^+(CH_3)_2$), 6.60–7.30 (m, 2, C_4 CH_2), 7.42 (s, 3, NCH_3), and 7.68–9.04 (m, 8, other protons).

Anal. Calcd for $C_{11}H_{23}N_2I$: C, 42.59; H, 7.47; N, 9.03. Found: C, 42.67; H, 7.09; N, 8.96.

15 was also obtained by direct methylation of **7** with methyl iodide in the presence of sodium hydride in benzene in 18% yield.

7,9-*exo*-Ethano-3,10-dimethyl-3,10-diazabicyclo[4.3.1]decanium Iodide (21).—A mixture of 0.09 g (0.5 mmol) of **12** and 0.22 g (1.5 mmol) of methyl iodide in 10 ml of dry benzene was stirred at room temperature for 30 min. Removal of the solvent and excess methyl iodide gave a brownish residue which on treatment with Norit A in ethanol afforded 0.027 g (43%) of **21** as a colorless prism: mp 173–175°; ir (KBr) 3270, 2925, 2780, 1470, and 1341 cm^{-1}; nmr (D_2O) τ 6.10–6.95 (m, 6, C_1 H, C_6 H, C_2 CH_2, and C_4 CH_2), 7.03 and 7.12 (each s, 6, $2NCH_3$), 7.50–8.10 (m, 5, C_7 H, C_9 H, C_8 endo H, and C_5 CH_2), 8.24 (broad s, 4, 7,9-ethano bridge), and 8.43–8.90 (m, 1, C_8 exo H).

Anal. Calcd for $C_{12}H_{23}N_2I$: C, 44.73; H, 7.19; N, 8.69. Found: C, 44.44; H, 7.05; N, 8.56.

Registry No.—**4**, 3371-52-6; **5**, 29584-53-0; **6**, 29661-05-0; **7**, 29584-54-1; **7** picrate, 29584-55-2; **9**, 29577-62-6; **11**, 29577-63-7; **12**, 29577-64-8; **15**, 29584-56-3; **19**, 29584-57-4; **21**, 29577-65-9.

Studies in Nonpyridinoid Aza-Aromatic Systems. I. The Synthesis and Tautomeric Character of Cyclopenta[*b*]quinoline (Benzo[*b*][1]pyrindine)[1]

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The synthesis of the tautomeric benzo[*b*][1]pyrindine (**3**) from 2,3-dihydro-1*H*-cyclopenta[*b*]quinoline (**4**) has been accomplished by three routes: (a) metalation with C_6H_5Li, oxidation to the 3-hydroxy derivative, and dehydration under well-defined conditions; (b) bromination to yield the 1-bromo or 3-bromo derivative, hydrolysis, and dehydration; and (c) N-oxidation, acetoxylative reduction, and dehydration. Compound **3** is a purple liquid consisting of 67% of the 1-H, 33% of the 3-H, and 0.1% of the 4-H tautomer. The small content of the 4-H tautomer belies its important role in determining the striking color of **3** and its chemical reactivity in response to electrophiles. The physical properties of **3** are assessed in the light of existing knowledge concerning the structure of pyrindines.

Armit and Robinson first recognized the significance of the aromatic sextet[2] through a study of the indenoquinoline system, where a cationic *N*-alkylpyridinium ring is fused to a ring bearing anionic cyclopentadienyl character (**1**). Subsequent developments in the theory of aromaticity[3,4] have led chemists to recognize this pyrindine system (**1**) as a nitrogen isostere of azulene. Although the substituted tautomers and derivatives of 1,5-pyrindine (**1**) and 2,5-pyrindine (**2**) have been known for some time,[5–8] the highly labile, parent N-substituted pyrindines have been isolated or detected only relatively recently.[9,10] The unsubstituted benzopyrindines, on the other hand, have not been reported in the literature, although unsuccessful synthetic attempts leading to other valuable substituted ones have been recorded.[7,8,11,12] For none of the pyrindines has a careful study of the N–H and C–H tautomers been made, nor is much known of the chemistry of the pyrindines or their relatives. The present article reports the first synthesis of the novel, unsubstituted benzo[*b*][1]pyrindine (cyclopenta[*b*]-quinoline[13]), gives the first complete spectral characterization of the tautomers of a pyrindine, and evaluates several interesting alternatives for obtaining

(1) Presented at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 10–14, 1967, Abstracts O-180.

(2) J. W. Armit and R. Robinson, *J. Chem. Soc.*, **121**, 827 (1922); *ibid.*, **127**, 1604 (1925).

(3) E. Hückel, *Z. Physik.*, **70**, 204 (1931); *ibid.*, **76**, 628 (1932).

(4) (a) D. Ginsburg, Ed., "Non-Benzenoid Aromatic Compounds," Interscience, New York, N. Y., 1959; (b) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, pp 256–304; (c) M. E. Vol'pin, *Russ. Chem. Rev.*, **29**, 129 (1960); (d) D. Lloyd, "Carbocyclic Non-Benzenoid Aromatic Compounds," Elsevier, New York, N. Y., 1966.

(5) W. Borsche, *Justus Liebigs Ann. Chem.*, **377**, 120 (1910).

(6) (a) V. Prelog and S. Szpilfogel, *Helv. Chim. Acta*, **28**, 1684 (1945); (b) V. Prelog and O. Metzler, *ibid.*, **29**, 1170 (1946).

(7) M. Los and W. H. Stafford, *J. Chem. Soc.*, 1680 (1959).

(8) W. Treibs and G. Kempter, *Chem. Ber.*, **92**, 601 (1959).

(9) A. G. Anderson, Jr., W. F. Harrison, R. G. Anderson, and A. G. Osborne, *J. Amer. Chem. Soc.*, **81**, 1255 (1959).

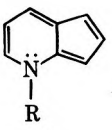
(10) (a) A. G. Anderson, Jr., and H. L. Ammon, *Tetrahedron Lett.*, 2579 (1966); (b) A. G. Anderson, Jr., and H. L. Ammon, *Tetrahedron*, **23**, 3601 (1967).

(11) W. Treibs, *Naturwissenschaften*, **49**, 37 (1962).

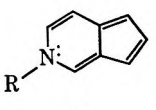
(12) L. E. Kholodov, I. F. Tishchenkova, and V. G. Yashunskii, *Tetrahedron Lett.*, 1535 (1970).

(13) Systematic name recommended by *Chemical Abstracts* and "Ring Index."

tautomeric cyclopenta[*b*]quinolines (**3a–c**) from their dihydro derivative (**4**). Subsequent papers will explore the chemistry of the azulenoid, aromatic system (**3c**) (R = alkyl or anion).



1



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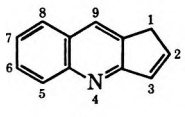
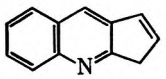
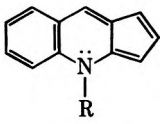


3a



3b



3c

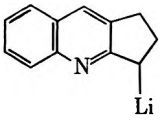
Results

Although we undertook the synthesis of a benzo derivative of 1-pyrindine (R = H) in the hope of obtaining a pyrindine of superior stability, these expectations were only partly realized. The most convenient starting material for the synthesis of **3** was the 2,3-dihydro derivative (**4**, β-quinindane) of **3a**, available from a Pfitzinger reaction between isatin and cyclopentanone and the thermal decarboxylation of the resulting 2,3-dihydro-1*H*-cyclopenta[*b*]quinoline-9-carboxylic acid (**5**).[5] In exploring methods of introducing a double bond into the five-membered ring of **4**, bromination was attempted under both free-radical and polar conditions. In the former method, **4** reacted with *N*-bromosuccinimide in carbon tetrachloride to yield 57% of a labile, monobromo derivative **6** (mp 84–86°) that proved too unstable to be analyzed. Because of its apparent homogeneity and its hydrolysis to yield the 1-hydroxy derivative **7** of **4**, it is concluded that bromination occurred preferentially at the 1-methylene group of **4**. On the other hand, bromination of **4** with 1 equiv of bromine in a warm solution of glacial acetic acid containing anhydrous sodium acetate gave a labile monobromo derivative (**8**, mp 125–127°) that could be hydrolyzed with ethanolic–aqueous silver nitrate solution to yield the 3-hydroxy derivative **9** of **4**.[14] The identities of the 1-hydroxy (**7**) and 3-hydroxy (**9**) derivatives rest on their analytical data, their nmr spectra which support a CHOH group adjacent to an aromatic ring (exclusion of the 2-hydroxy derivative), and the independent synthesis of the 3-hydroxy derivative **9** in two well-precedented ways (*cf. infra*). These observed preferential brominations are consistent with the views that free-radical abstraction of hydrogen is more rapid at C-1 (adverse polar effect[15]) (**10**) and that bromination in acetic acid may proceed through enaminization (**11**) (Scheme I).

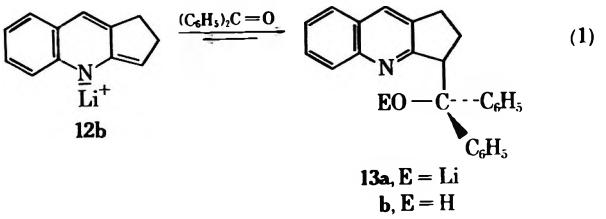
Previous mention of the monobromo derivative obtained from **4** and *N*-bromosuccinimide had assumed that it was the 3 isomer,[7] but no chemical or physical characterization was reported.

Ultimately, however, both brominations have proved impractical for the preparation of the 1- or 3-hydroxy precursors of the desired benzo[*b*][1]pyrindine (**3**). The hydrolyses of the 1-bromo and 3-bromo derivatives **6** and **8** were always overshadowed by side reactions leading to intractable gums and black solids. Even the attempt to dehydrohalogenate the 1-bromo derivative **6** directly, with sodium iodide in dimethylformamide at room temperature, led only to decomposition.

The preferential introduction of substituents at the 3 position of β-quinindane **4** could be achieved *via* its lithium salt **12**, which could be prepared in essentially quantitative yield by treating **4** with 1 equiv of phenyllithium in diethyl ether.[16] The lithium enaminate salt, presumably better formulated as a contact ion pair centered on nitrogen (**12b**), rather than as an organolithium reagent at C-3[17] (**12a**), underwent solely C-alkylation both with ketones and with methyl iodide (eq 1). The interaction of **12b** with benzo-

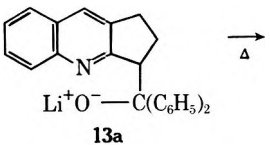


12a

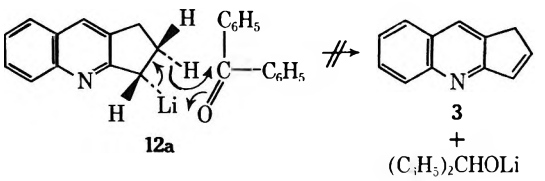


12b **13a**, E = Li; **b**, E = H (1)

phenone was shown to be reversible, for the treatment of the pure, isolated 2,3-dihydro-α,α-diphenyl-1*H*-cyclopenta[*b*]quinoline-3-methanol (**13b**) with 1 equiv of phenyllithium, forming **13a**, led to the detection of **4** and benzophenone upon hydrolytic work-up. The reversible dissociation of **13a** into its components thus limited the yield of carbinol to *ca.* 70%. The reversibility of the reaction, **12** ⇌ **13a**, was of great interest, since it was felt that the lithium salt **12** might eventually react with benzophenone in an alternative manner (eq 2), namely by hydride transfer.



13a



12a **3** + $(C_6H_5)_2CHOLi$ (2)

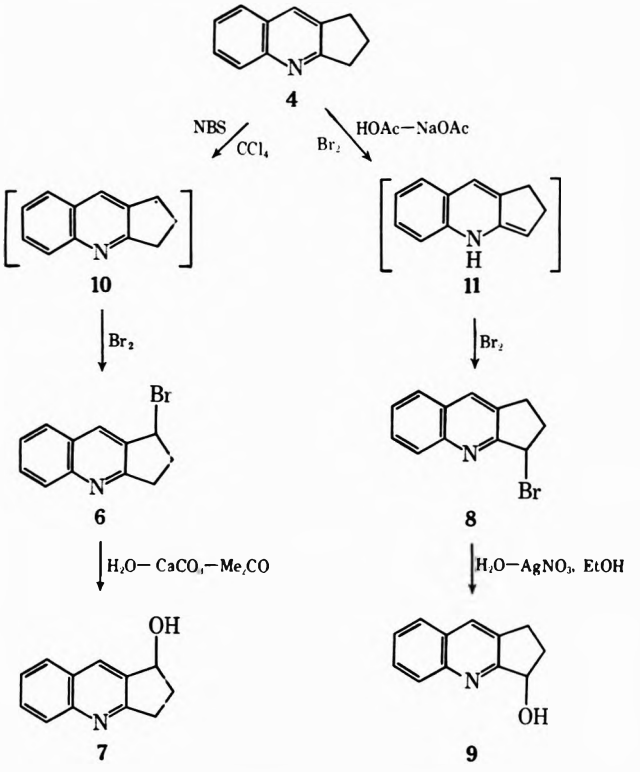
(14) J. J. Eisch and K. C. Fichter, unpublished studies.

(15) In a Hammett study of the relative reactivities of substituted toluenes toward *N*-bromosuccinimide, E. C. Kooyman, R. Van Helden, and A. F. Bickel [*Kon. Ned. Akad. Wetensch. Proc., Ser. B*, **56**, 75 (1953)] showed that bromination occurred preferentially at points of high electron availability: a plot of log reactivity *vs.* σ gave ρ of −1.55. As a specific precedent for the behavior of **4**, the behavior of 1,5-diphenyl-1-pentanone toward *N*-bromosuccinimide can be cited; attack at the methylene next to the phenyl, rather than next to the carbonyl, is observed.

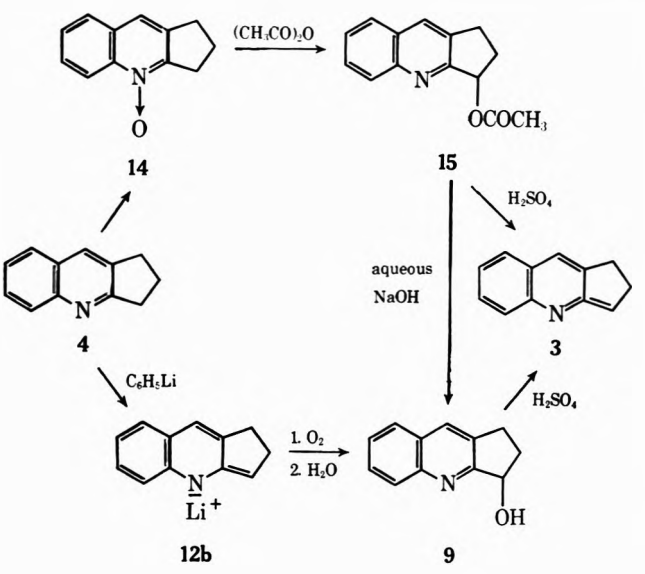
(16) K. Ziegler and H. Zeiser, *Justus Liebigs Ann. Chem.*, **485**, 174 (1931), achieved almost complete α metalation of both 2-methylpyridine and 2-methylquinoline by use of phenyllithium.

(17) *Cf.* G. Stork and S. R. Dowd, for the C-alkylation of the magnesium salts of N-substituted imines. The colors observed for **12b** and **16** fit the view that extensive charge delocalization occurs in such π systems with much charge on nitrogen. One might speculate that the failure of **12** to lose lithium hydride (eq 2) is a further indication that **12b** is a more accurate representation than **12a**.

SCHEME I



SCHEME II



The interaction of benzophenone with various alkyl Grignard reagents to yield benzhydrol and alkene[18a] suggested that the reversal of **13a** into its components might lead tc the desired benzo[*b*][1]pyrindine (**3**) and benzhydrol.[18b] However, prolonged refluxing of **13a** suspended in ether or in benzene gave no indication of the formation of benhydrol or **3**.

Despite the failure of the lithium salt **12** to serve as a source of the benzo[*b*][1]pyrindine *via* hydride transfer, its treatment with molecular oxygen proved to be a convenient route to the 3-hydroxy-β-quinindane **9**, albeit in modest yield. An alternative route to this hydroxy derivative was a three-step sequence involving the N-oxidatione of β-quinindane, treatment of the resulting *N*-oxide **14** with acetic anhydride, and the saponification of the 3-acetoxy derivative **15** (Scheme II). The assignment of the structure of the hydroxy-β-quinindane as the 3 isomer is supported by the known tendency of both phenyllithium[16] and acetic anhydride[19,20] to attack the α-methylene hydrogens of their respective pyridine substrates.

The foregoing preparations of the 1-hydroxy and 3-hydroxy derivates of β-quinindane **7** and **9** now permitted attempts at their dehydration for the formation of the benzc[*b*][1]pyrindine system (**3**). Although 7-hydroxy-6,7-dihydro-1,5-pyrindine or its acetate is reported to give an 88% yield of 1,5-pyrindine by dehydration with concentrated sulfuric acid during 1 hr at 120–130°,[20] such conditions were far too severe for the dehydration or the dehydroacetoxylation of **7**, **9**, or **15**. Milder dehydration procedures, such as traces of strong acids (sulfuric or *p*-toluenesulfonic) in warm acetic acid or benzene, proved to be ineffectual and stronger acids tended to produce polymeric materials. Only by short-term exposure (3–5 min) to concentrated sulfuric acid preheated to 120° and by immediate quenching on ice could a satisfactory yield of **3** be obtained. Even with such control, only the 3-hydroxy (**9**) or the 3-acetoxy **15** derivative gave satisfactory yields of **3** (50–60%); the 1-hydroxy derivative **7** was more prone tc side reactions and afforded only traces of **3**.

The benzo[*b*][1]pyrindine (β-quinindene, **3**) proved to have gratifyingly unusual properties. The compound was obtained, upon distillation, as a deep purple oil, which upon chilling crystallized to a pure white solid. The solid β-quinindene had a melting point almost identical with that of β-quinindane **4**; its ability to undergo repeated melting to a purple oil and resolidification to a white solid appears to be an example of thermochromism.[21] Although this β-quinindene could be stored unchanged under a nitrogen atmosphere below 0° for several days, exposure to oxygen and temperatures above 60° tended to promote decomposition.

The spectral properties of this benzo[*b*][1]pyrindine (**3**) showed that it was a mixture of the three tautomers, 1-H (**3a**), 3-H (**3b**), and 4-H (**3c**, R = H), in proportions varying with the physical state, temperature, time, and treatment of the sample. An infrared spectrum of the neat, supercooled purple oil displayed an N–H absorption of medium intensity at 2.9 μ; in a 10% solution in carbon tetrachloride this absorption had almost completely disappeared. The visible spectrum of a pink 1.94 *M* solution of **3** in benzene at 25° displayed one broad absorption from 470 to 540 mμ, centered at 507 mμ. The ultraviolet absorption spectrum of **3** in cyclohexane, in comparison with that of β-quinindane **4** displayed the expected bathochromic shift: absorptions for **4** at λ_{max} 237 mμ (log ε 4.58), 305 (3.75), and 319; for **3** at 246 mμ (log ε 4.67), 297 (3.90), 318 (3.87) and 332 (3.99). In a 0.01 *N* solution of hydrochloric acid in 95% ethanol the β-quinindane **4** had absorption maxima at 244 mμ (log ε 4.55) and 319 (4.05) and the β-quinindene **3** at 230 mμ (sh, log ε 5.03), 259 (4.80), 280 (sh, 4.45),

(18) (a) M. S. Kharasch and S. Weinhouse, *J. Org. Chem.*, **1**, 209 (1936); (b) *cf.* H. Gilman and C. W. Bradley, *J. Amer. Chem. Soc.*, **60**, 2335 (1938), for the ready loss of lithium hydride from organolithium compounds.

(19) (a) V. Boekelheide and W. L. Linn, *ibid.*, **76**, 1286 (1954); (b) O. H. Bullit and J. T. Maynard, *ibid.*, **76**, 1370 (1954).

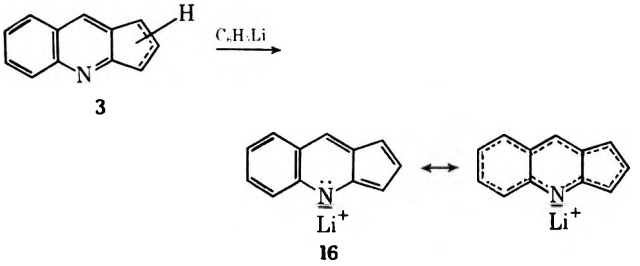
(20) M. M. Robinson, *ibid.*, **80**, 6254 (1958).

(21) J. H. Day, *Chem. Rev.*, **63**, 65 (1963).

312 (4.28), and 332 (4.30). The nmr spectrum of **3** in carbon tetrachloride (25% by weight) showed two distinct methylene signals, each having small hyperfine splittings, at δ 3.48 (A) and 3.22 (B) ppm, respectively. The areas of signals A and B were taken as measures of the ratio of 3*H*-benzo[*b*][1]pyrindine (**3b**) to 1*H*-benzo[*b*][1]pyrindine (**3a**), since the methyl group in α-picoline absorbs at a lower field (2.6 ppm) than the methyl group in β-picoline (2.2 ppm).[22] A freshly distilled sample of **3** showed in carbon tetrachloride a 3-H:1-H tautomeric ratio of 45:55; after 72 hr at 0° the ratio had changed to 33:67. This ratio (±2 parts) seems to be the thermodynamically stable mixture at 25° (*cf. infra*).

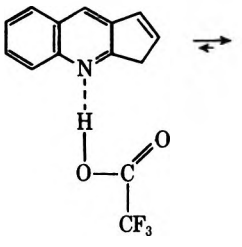
The nmr spectral data give a ready measure of the proportion of the two isomers, **3a** and **3b**, showing that **3a** is more stable than **3b** by *ca.* 450 cal. The absence of any infrared or nmr evidence for the existence of a considerable amount of 4*H*-benzo[*b*][1]pyrindine (**3c**, R = H) in moderately concentrated solutions suggests that less than 1% of **3c** was present. The presence of 0.093% of **3c** in a 1.94 *M* solution of benzo[*b*][1]pyrindine in benzene was estimated by visible spectroscopy. The assumption was made that the extinction coefficient for a corresponding band in the similar, isoelectronic 5,6-benzazulene system[23] could be used for tautomer **3c** (ϵ 316 for the 557-mμ band). Accordingly, one can estimate that tautomers **3a** and **3b** are at least 4 kcal more stable than isomer **3c**.

The proportion of the 1*H*- and 3*H*-benzo[*b*][1]pyrindine tautomers, **3a** and **3b**, was also dependent upon the chemical treatment of the sample or upon the solvent in which the nmr spectrum of tautomeric mixture **3** was recorded. Treatment of **3** with 1 equiv of phenyllithium at 0° resulted in the formation of the blood-red lithium salt **16** which, as with the lithium salt of β-quinindane **12b**, seems best formulated as an enaminate ion-pair salt. The visible spectrum of **16**, a

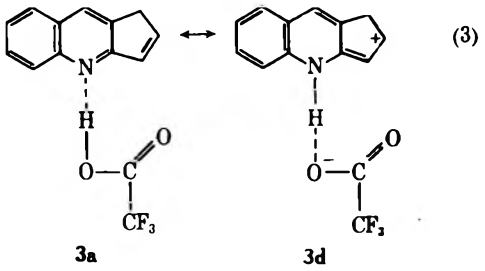


solution of which was prepared by adding 1 equiv of *n*-butyllithium in hexane to **3** dissolved in benzene, has three broad maxima at λ_{max} 468 mμ (log ϵ 2.99), 497 (3.01), and 530 (2.94). Hydrolysis of **16** after a short-term storage at 0° yielded recovered **3** having 31% of the 1-H tautomer (**3a**) and 69% of the 3-H tautomer (**3b**). Reasonable agreement between this base-equilibrated ratio and the ratio of tautomers achieved eventually by storage of **3** (*cf. supra*) verifies that the two tautomers were present in their equilibrium proportions.

The chemical shifts and the separation of methylene signals A (**3b**) and B (**3a**) were dependent upon the solvent (solvent, A, B, and A–B in ppm): neat 3.56, 3.04, and 0.52; CCl_4 (26% wt) 3.42, 3.16, and 0.26; CCl_4–NMe_3 (31% wt) 3.57, 3.42, and 0.15; CF_3COOH (52% wt) 4.24, 4.06, and 0.18; and C_6H_5Br (6% wt) 3.12, 2.86, and 0.26. Although the ratio of A:B did not change significantly in most of these solvents [typical ratio for freshly distilled sample, (45 ± 3):55], the proportion A:B in trifluoroacetic acid was 23:77. Furthermore, these methylene peaks were shifted downfield by 0.8–0.9 ppm, had lost all hint of hyperfine structure, and no longer displayed base-line separation. These observations can be interpreted to mean that protonation or hydrogen bonding of **3** by trifluoroacetic acid further favors the formation, at equilibrium, of tautomer **3a** because of available charge delocalization (**3d**). The narrowing and incipient merging of the



3b



3a **3d** (3)

methylene signals, moreover, suggested that the rate of tautomer interconversion had increased in this acidic medium. In an analogous attempt to accelerate the interconversion of tautomers **3a** and **3b**, trimethylamine was added to a CCl_4 solution of **3**. The decrease in the separation of the signals A and B (0.26 → 0.15 ppm) suggests that the rate had increased somewhat. Complete coalescence of these signals, by heating these acidic or basic solutions by or heating a solution of **3** in bromobenzene, could only be achieved under conditions (>100°) where irreversible chemical change occurred. Presumably such systems, being at once analogs of 2-vinylpyridine and cyclopentadiene, eventually undergo auto-Michael reactions,[24] as supported by the broad nmr signal in the 3.0–3.5-ppm region of decomposed material.

Discussion

A comparison of the benzo[*b*][1]pyrindines (**3a–c**, R = H) with the known 1,5-pyrindine tautomeric mixture (*i.e.*, **1**, R = H, and its tautomers) is in order. The amounts of the N-H tautomer, 0.093% for a 1.9 *M* viclet solution of **3** in benzene *vs.* 0.11% for a neat orange sample of **1**,[25] are estimated by different methods, namely assumptions concerning the ultraviolet extinction coefficient of **3c** and **1** and a pK_a estimate of the basicities of the 1-H and 5-H tautomers of **1**, respectively. In the latter pK_a method no ac-

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(25) C. B. Reese, *ibid.*, **84**, 3979 (1962).

count was taken of the varying amounts of the 5-H and 7-H tautomers of **1**.[25] With these limitations in mind, one can conclude that the amount of N–H tautomer for a neat sample of **3** would be greater than that of **1**, since a solution of **3** is already comparable to neat **1**. The deep purple color of melted **3** confirms this assumption. However, the nmr spectrum of **3**, even in concentrated form, gave no sign of an N–H peak ascribable to **3c** in the region of 3.6–4.7 ppm,[26] but this is not surprising in view of the small amount present. The superior sensitivity of a visible spectral estimate for this azulene-like tautomer (azalene **3c**) is also seen in the fact that even a 0.01% solution of azulene itself is highly colored.[27]

The assignment of this purple-colored component as the N–H tautomer (**3c**, R = H) was supported by the observed blood-red color of the analogous lithium salt **16** in ether–benzene and the purple color of anions of 3-substituted benzo[*b*][1]pyrindines in tetrahydrofuran.[28] Quaternizing **3** with methyl iodide and then treating the salt with sodium carbonate does give a purple species, presumably **3c** (R = CH_3).[28] With the pyrindine system there is disagreement as to whether this procedure leads to **1** (R = CH_3).[10b,25] A difficulty with this method, possibly overlooked in the pyrindine system,[10b,25,29] is that methylation occurs both on nitrogen (82%) and on the α-carbon atom (18% on C_3 in **3**).[28] C-Alkylation can most reasonably be attributed to β (C_3) electrophilic attack on the enamine tautomer **3c** (R = H).

The present nmr data on **3** demonstrate, for the first time, the relative stability of C–H tautomers of a pyrindine system. Attempts to make such a distinction based upon differences in ultraviolet absorptions were unsuccessful.[29,30] The recorded nmr spectrum of 1-pyrindine does show some slight favoring of the 5-H tautomer over the 7-H, by our visual estimation, but the significance of this spectral information has not been pointed out.[29] Moreover, no data were given on the length of time between the preparation of the pyrindine and the spectral measurement. With the benzo[*b*][1]pyrindine, the equilibrium mixture at 25° contains 67 ± 2% of the 1-H tautomer **3a**. Protic or hydrogen-bonding media, such as trifluoroacetic acid, enhance the amount of **3a** (eq 3). Furthermore, the bathochromic shift in the ultraviolet spectrum of **3**, especially in acidic solution, can be ascribed principally to the importance of polar resonance forms, such as **3d**, available to the predominant tautomer **3a**.

The visible spectra of 4H-benzo[*b*][1]pyrindine (**3c**) and its lithium salt **16** show pronounced bathochromic shifts when compared with spectra of 1-pyrindine (**1**, R = H or CH_3). Recent quantum mechanical calculations predicted that such a shift would be observed.[31] Comparison of the spectral shapes of 5,6-benzazulene[23,32] and **3c** shows that both have similar broad absorptions at >500 mμ, with **3c** peaking some 50 mμ below that of the azulene. Visible spectra of substituted benzo[*b*][1]pyrindines have been known to resemble that of 5,6-benzazulene rather closely.[7,8] The lithium salt **16** has a visible maximum only 27 mμ below that of 5,6-benzazulene, but its absorption drops more sharply above 550 mμ.

The question of the rate of interconversion of the 1-H and 3-H tautomers of **3** in acidic or basic media cannot be answered definitively. In trifluoroacetic acid the methylene signals lost both their fine structure and base-line separation. The recorded spectrum of 1-pyrindine in this medium displays such coalescence of methylene signals, although the author does not comment on its significance.[29] It would appear that the exchange of protons between the C_1 and C_3 sites in benzo[*b*][1]pyrindine and between the C_5 and C_7 sites in 1-pyrindine become significant in this medium. Analogous attempts to observe coalescence by heating **3** itself, or with triethylamine, were indicative of some accelerated proton exchange, but their success was limited by the decomposition of **3**. As with the well-studied indene system,[33,34] such proton exchange may well occur by an intramolecular route.

Although the nature of the thermal decomposition products of **3** is not completely clear, existing evidence suggests that a Michael reaction of enamine **3c** or its anion **16** occurs with the 1-H tautomer, itself a vinylic pyridine.[24] The facility of such an allylic carbanion attack on a vinylpyridine is seen in the smooth 1,4 addition of allylmagnesium bromide to *trans*-2-phenylvinylpyridine (2-stilbazole).[35]

Ongoing research is concerned with evaluating the aromatic character of the N–H tautomer of benzo[*b*][1]-pyrindine and its delocalized anion,[26] with an eye to the azulene-like character of these systems.

Experimental Section

Melting points were determined with a Thomas-Hoover "Unimelt" apparatus and are corrected. Infrared spectra were recorded of samples as potassium bromide disks, mineral oil suspensions, or solutions in pure solvents, by means of a Perkin-Elmer spectrophotometer, Model 139. Proton magnetic resonance spectra were measured with a Varian spectrometer, Model A-60, on samples dissolved as 10% solutions in pure solvents containing tetramethylsilane as an internal standard. Signals are reported using the δ scale in parts per million, followed by the integrated intensities of the proton signals and the coupling constants (J) in hertz. Ultraviolet and visible spectral data were obtained with a Cary spectrophotometer, Model 15, on samples dissolved in cyclohexane, benzene, or 95% ethanol of "spectral-grade" purity. Vpc analyses were performed on an F & M dual-column chromatograph equipped with 2-ft columns packed with 10% silicone gum rubber on firebrick. Tlc plates were prepared with silica gel, developed usually with methylene chloride and then sprayed with chromic acid solution for detection of the separated components. Elemental analyses were carried out by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

All preparations and reactions involving either air- and moisture-sensitive organometallic reagents or reactive heterocyclic intermediates were conducted under an atmosphere of dry, oxygen-free nitrogen. Appropriate techniques for such manipulations, including the necessary purification of solvents, have already been described.[37]

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(27) W. Baker and J. F. W. McOmie in "Progress in Organic Chemistry," Vol. 3, J. W. Cook, Ed., Academic Press, New York, N. Y., 1955, p 44.

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(36) J. J. Eisch, C. Kovacs, and C. T. Kuo, unpublished studies.

(37) J. J. Eisch and W. C. Kaska, *J. Amer. Chem. Soc.*, **88**, 2213, 2976 (1966).

Reagents.—The known 2,3-dihydro-1*H*-cyclopenta[*b*]quinoline-9-carboxylic acid (**5**) was prepared in large-scale runs of 1–3 mol by adapting a published Pfitzinger reaction involving isatin and cyclopentanone in a basic medium. Although a 90% yield of crude acid **5** was obtained, the melting range (230–260°) and the subsequent decarboxylation products betrayed the presence of the 3-cyclopentidylidene derivative of **4**. The impurity presumably arose from the participation of 2-cyclopentylidenecyclopentanone, the aldol condensation product of the starting ketone, in a competing Pfitzinger reaction.[5,38]

2,3-Dihydro-1*H*-cyclopenta[*b*]quinoline (**4**) was prepared by the thermal decarboxylation of **5** at 250–300° (sand bath) and by the fractional distillation of the residue: the first main fraction, bp 106–108° (0.25 mm), was colorless **4**, which solidified on standing; the second main fraction was a yellow oil, bp 157–159° (0.70 mm), which by spectral data was thought to be the cyclopentylidene derivative of **4** (5% yield). The first fraction was dissolved in ether and the resulting solution extracted with 5% sodium hydroxide solution, washed with water, and dried over anhydrous calcium sulfate. After removal of ether the residual **4** was recrystallized from petroleum ether (bp 30–60°) to yield colorless crystals of **4**: mp 59–61° (lit.[5] 59–60°); spectral data nmr (CS_2) 1.90–2.52 (m, 2-CH_2) 2.90–3.45 (m, 1-CH_2, 3-CH_2), 7.5–8.38 (m, 5 H).

Lithium Salt of 2,3-Dihydro-1*H*-cyclopenta[*b*]quinoline (12).—To a solution of **4** (8.45 g, 50.0 mmol) in 100 ml of dry benzene were added dropwise 55 mmol of phenyllithium in 60 ml of ether, while the reagents were stirred in a bath of ice water. Upon adding the first few drops of the phenyllithium reagent, a vivid red color appeared, but this faded as the addition continued. The Gilman color test I remained negative[39] until an excess of phenyllithium had been added. The tan-colored suspension was allowed to come to room temperature over a 3-hr stirring period. Then a solution of 11.4 g (62.5 mmol) of benzophenone in 100 ml of dry benzene was added dropwise over a 45-min period. The color of the reaction mixture lightened and a noticeable exotherm occurred. After a further 2-hr stirring period, the suspension was hydrolyzed with 150 ml of saturated sodium bicarbonate solution. Usual work-up, drying of organic extract, and removal of solvent left the crude carbinol, which upon recrystallization from methylene chloride yielded 12.4 g (71%) of 2,3-dihydro-α,α-diphenyl-1*H*-cyclopenta[*b*]quinoline-3-methanol (**13b**), mp 152–154°. An analytical sample melted at 154–155.5°: ir $\lambda_{max}^{CH_2Cl_2}$ 2.95 μ (OH).

Anal. Calcd for $C_{25}H_{21}NO$: C, 85.43; H, 6.02. Found: C, 85.35; H, 6.01.

Although **13b** suffered no cleavage, *via* reverse aldol reaction, into **4** and benzophenone when chromatographed on neutral alumina with a benzene eluent, cleavage did occur during tlc on silica gel. Even during successful acid-catalyzed dehydration of **13b** to produce 2,3-dihydro-3-diphenylmethylene-1*H*-cyclopenta[*b*]quinoline, some reverse aldol cleavage was detected. This cleavage also occurred when pure **13b** was treated with 1 equiv of phenyllithium and the mixture then worked up. The demonstrated ease with which the lithium salt **12** reacts reversibly with benzophenone clearly puts a limit on the yield of isolable carbinol **13b**. Since treatment of **12** with methyl iodide gave a >90% isolated yield of the 3-methyl derivative of **4**, the formation of **12** from **4** and phenyllithium must proceed almost quantitatively.

2,3-Dihydro-3-hydroxy-1*H*-cyclopenta[*b*]quinoline (9) from 4.—According to the foregoing procedure, proportional amounts of **4** and phenyllithium in ether were used to prepare 400 mmol of the lithium salt **12** in 1000 ml of dry benzene. With cooling at −15° and vigorous stirring a stream of dry oxygen gas was bubbled through the suspension over a 4-hr period. After being stirred overnight at room temperature, the reaction suspension was hydrolyzed with 1 *N* hydrochloric acid and the liquid layers were separated from residual solids by filtration. The separated aqueous layer was made basic with 5% sodium hydroxide solution and the precipitated organic bases were taken up in ether. Drying of the ether extract, removal of solvent, and washing the residue with cyclohexane left 23 g (31%) of crude **9**. Recrystallizations from cyclohexane–petroleum ether (bp 30–60°) gave the pure 3-hydroxy derivative **9** as pale yellow cubic crystals, 9.6 g (13%), mp 128–129°. Several variations in the oxidation procedure did not improve the yield: spectral data ir $\lambda_{max}^{mineral\ oil}$ 3.10 μ (OH); nmr ($CDCl_3$) 2.50–3.2 (m, 2-CH_2, 1-OH), 3.50–3.70 (m, 1-CH_2), 5.70–6.0 (m, 3-CH).

Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.98. Found: C, 77.74; H, 6.05.

3-Acetoxy-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline (15).—Water (0.42 g, 24 mmol) was added to a mixture of 5.2 g (500 mmol) of acetic anhydride and 6.51 g (30 mmol) of 2,3-dihydro-1*H*-cyclopenta[*b*]quinoline *N*-oxide (**14**).[40] After a slightly exothermic reaction had occurred, the mixture was heated on a boiling water bath for 1.5 hr. After concentrating and cooling, the solution was taken up in ether and made basic by treatment with a 5% sodium carbonate solution. The ether layer was separated, dried over anhydrous potassium carbonate, and freed of volatile solvent. Recrystallization of the residual dark oil from petroleum ether gave light yellow, rod-like clusters of the 3-acetoxy derivative **15**: mp 106–108°; 5.6 g (81%); ir λ_{neat}^{KBr} 5.70 μ; nmr ($CDCl_3$) 2.26 (s, 3 H), 2.4–3.0 (m, 2-CH_2), 3.1–3.5 (m, 1-CH_2), 6.3–6.5 (m, 3-CH_2), 7.6–8.2 (4 H), 8.3–8.5 (m, 5-CH).

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.76; N, 6.10. Found: C, 73.88; H, 5.65; N, 6.20.

This compound could be saponified to yield the aforementioned 3-hydroxy derivative **9**, by heating a mixture of **15** (850 mg, 3.7 mmol), sodium hydroxide (200 mg), and water (1.8 g) on a boiling water bath for 15 min. The mixture was cooled, saturated with potassium carbonate, and extracted with several portions of chloroform. The combined chloroform extracts were passed through a short column of alumina and the resulting eluate was evaporated to dryness. Recrystallization of the residue from cyclohexane–petroleum ether (bp 30–60°) yielded 41% of pure **9**, identical by ir and nmr spectral and mixture melting point criteria with the oxidation product of the lithium salt **12**.

1*H*- (or 3*H*- or 4*H*-) Cyclopenta[*b*]quinoline (Benzo[*b*][1]-pyridine) (3).—The procedure given here had to be followed strictly, in order to obtain satisfactory yields of **3**. Other procedural variants and other methods of dehydration (trace of sulfuric acid in glacial acetic acid, 85% *o*-phosphoric acid, or *p*-toluenesulfonic acid in warm benzene[41]) proved to be unsatisfactory.

Over the course of 20 min the powdered 3-hydroxy derivative **9** (3.00 g, 16.2 mmol), or an equivalent amount of the 3-acetoxy compound **15**, was dusted into 35 ml of cooled, concentrated sulfuric acid contained in a flask equipped with a motor-driven stirrer. The orange-brown solution was immediately thereupon immersed in an oil bath maintained at 120–130°, heated for 4 min, and promptly poured over 300 g of ice. While the thawed solution was kept below 30°, a 50% aqueous solution of sodium hydroxide (150 g) was slowly added. The organic precipitate was taken up in ether and the ether extract, after extraction with water, was dried over anhydrous potassium carbonate. A trace of hydroquinone was added to the extract and the entire purification was executed promptly, in order to minimize decomposition. With very slight warming the solvent was removed with a rotary evaporator and the residual brown oil immediately distilled at reduced pressure in an apparatus previously flushed with nitrogen. The dehydration product **3** distilled over as a violet-colored oil, bp 130–132° (1.3 mm), 1.5 g (50%). This substance gradually solidified to an almost colorless substance, mp 59–61° (sealed tube), and could be stored for several weeks without apparent decomposition if kept under nitrogen below 0°. Redistillation always was accompanied by considerable losses due to thermal dimerization or polymerization (nmr examination of the residue).

A further distillation provided an analytical sample, bp 115–116° (0.5 mm), which was shipped for analysis in a sealed, nitrogen-filled ampoule: spectral data ir λ_{max}^{neat} 2.9 (distinct NH), 6.15 and 6.35 μ (aromatic C=C with conjd C=C); $\lambda_{max}^{10\%\ CCl_4}$ essentially no distinct band at 2.9 μ; nmr (CCl_4) 3.16 (s, 1, 1-CH_2), 3.42 (s, 1, 3-CH_2), 6.40–7.16 (m, 2, 1-, 2- and 3-vinyl), 7.16–8.08 (m, 5, aromatic CH) (*cf.* Results for further details, such as the variation in the integrated intensities and the peak separations of the 1- and 3-methylene signals).

Anal. Calcd for $C_{12}H_9N$: C, 86.20; H, 5.42; N, 8.38. Found: C, 85.83; H, 5.40; N, 8.81.

The product formed a picrate readily (highest mp 215.5–217.5°, from ethanol) but the elementary analysis was not satisfactory, despite repeated attempts at purification (3.35% high on C, 1.21% low on N), nor were satisfactory derivatives ob-

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(39) H. Gilman and F. Schulze, *J. Amer. Chem. Soc.*, **47**, 2002 (1925).

(40) E. Hayashi and Y. Yamamoto, *Yakugaku Zasshi*, **87**, 1290 (1967).

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tained with chloroplantinic acid, picrolonic acid, 2,4,7-trinitrofluoren-9-one, or 1,3,5-trinitrobenzene. The presence of sensitive tautomeric components in **3** that are decomposed by acid and oxidizing agents may be at fault in these unfruitful reactions.

Lithium Salt of Cyclopenta[*b*]quinoline (Benzo[*b*][1]pyridine) (16).—The sensitivity of the cyclopenta[*b*]quinoline **3**, apparently to base-promoted autoaddition, demands that the reaction conditions described here be adhered to strictly or subsequent hydrolysis will permit no recovery of **3**.

Under a nitrogen atmosphere a solution of 1.31 g (7.86 mmol) of **3** dissolved in 50 ml of dry, degassed benzene was treated dropwise over 8 min with 7.92 mequiv of ethereal phenyllithium while stirring at 0° was maintained. Then the blood-red solution of lithium salt **15** was stirred for a further 10 min at 0° and then promptly hydrolyzed at 0° with degassed water and worked up in the usual way. Distillation gave a 28% recovery of **3**, as proved both by bp and by ir and nmr spectral data.

If the blood-red solution of **16** was allowed to stand at >20° for 1 hr and then worked up in the same manner, no **3** was obtained.

1-Bromo-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline (6).—To a stirred, refluxing solution of 8.45 g (50.0 mmol) of **4** in 150 ml of carbon tetrachloride were added 8.95 g (52.0 mmol) of colorless, pure *N*-bromosuccinimide, in portions, over the course of 45 min. The resulting suspension was heated at reflux for an additional 20 min, cooled, and filtered. With a minimum of warming the filtrate was freed of solvent under reduced pressure. The resultant dark residue was extracted promptly with six 50-ml portions of hot petroleum ether (bp 30–60°) and these combined extracts were then concentrated. Cooling of the extracts deposited 7.1 g (28.5 mmol, 57%) of yellow cubic crystals of 1-bromo-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline (**6**), mp 84–86°. This product appeared to be homogeneous (*i.e.*, one isomer) as judged by its melting point and ir spectrum, but its sensitivity to air and to heat prevented an elemental analysis or further purification. Its identity as the 1 isomer rests upon its subsequent hydrolysis, albeit in low yield, to the 1-hydroxy derivative of **4**.

The infrared spectrum of **6** in CS_2 showed strong bands at 3.15, 3.35, 6.15, 7.2, 8.5, 10.55, 11.15, 11.7, 12.2, 12.75, 13.4, and 13.9 μ.

2,3-Dihydro-1-hydroxy-1*H*-cyclopenta[*b*]quinoline (7).—A sample of the bromo derivative **6** (6.2 g, 25 mmol), prepared as described above and dissolved in 50 ml of acetone, was stirred for 1 hr at room temperature with a slurry of 5 g of powdered calcium carbonate in 25 ml of water. The reaction suspension was filtered and the filtrate concentrated by warming under reduced pressure. The residue was extracted with ether, the ether extract dried, and the solvent removed from the extract. Several recrystallizations of this residue from a cyclohexane–petroleum ether (bp 30–60°) pair gave almost colorless needles: 1.1 g (24%) of the 1-hydroxy derivative **7**; mp 166.5–168°; a test for halogen was negative; spectral data ir (mineral oil) 3.05 μ (OH), and strong bands at 6.15, 8.75, 9.15, 9.4, 10.9, 11.75, 12.75, and 13.2 μ; nmr ($CDCl_3$) 2.15 (m, 1, 1-OH), 2.3–2.9 (m, 2, 2-CH_2), 3.0–3.3 (m, 2, 3-CH_2), 5.25–5.6 (m, 1, 1-CH), 7.6–8.1 (m, 5, arom). The assignment of the multiplet at 2.15 to the 1-hydroxyl group was made upon the basis of the disappearance of this signal when a sample of in $CDCl_3$ was shaken with deuterium oxide.

Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99. Found: C, 77.71; H, 6.22.

Dehydration of 2,3-Dihydro-1-hydroxy-1*H*-cyclopenta[*b*]quinoline (7).—The dehydration of the 1-hydroxy isomer proved to be even more sensitive to further reaction than that of the 3-hydroxy isomer and hence was impractical for the preparation of benzo[*b*][1]pyrindine. Milder dehydrating agents for brief reaction periods, dimethyl sulfoxide at reflux, oxalic acid in hot aqueous solution, or phosphorus pentoxide in refluxing xylene, gave no dehydration; longer reaction times led to further reaction. Only with conditions similar to those used with 3-hydroxy isomer was any success achieved. Thus, when a 2.0-g sample of **7** was heated with 35 ml of concentrated sulfuric acid for 4 min and then worked up as before, distillation under reduced pressure afforded only a few drops of benzo[*b*][1]pyrindine (**3**), whose identity was established by ir and nmr spectral comparison.

Mass Spectra of 2,3-Dihydro-1-hydroxy-1*H*-cyclopenta[*b*]quinoline and of 2,3-Dihydro-3-hydroxy-1*H*-cyclopenta[*b*]quinoline.—Under a pressure of 10^{-6} Torr, a source temperature of 330° and electron energies of 70 eV, the following relative abundances (selected values) of ion fragments were observed—mass (abundance relative to the base peak): 1-hydroxy isomer, 185 (100), 184 (97), 169 (7), 168 (27), 167 (37), 157 (7), 156 (37), 155 (7), 154 (10), 140 (10), 139 (10), 130 (10), 129 (17), and 128 (23); 3-hydroxy isomer, 185 (45), 184 (16), 183 (13), 169 (70), 168 (68), 167 (45), 157 (78), 156 (100), 140 (11), and 129 (45).

Registry No.—**3a**, 268-85-9; **4**, 5661-06-3; **6**, 29411-23-3; **7**, 29411-24-3; **9**, 29411-25-4; **13b**, 29520-62-5; **15**, 29411-26-5.

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A Nuclear Magnetic Resonance Study of the Cyclohexane Ring Conformation in Selectively Deuterated Cis Isomers of 2-Piperidino-α-(p-methoxyphenyl)cyclohexanemethanol

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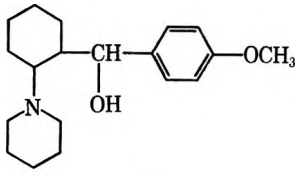
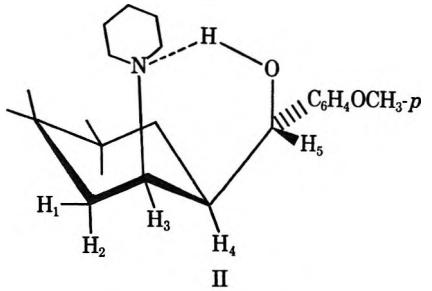
Selectively deuterated samples of the two cis isomers of 2-piperidino-α-(p-methoxyphenyl)cyclohexanemethanol have been synthesized to allow nmr investigation of the cyclohexane ring conformation. Isotopic substitution was effected at all positions in the piperidine ring and at carbons 4–6 of the cyclohexane ring in each compound. The four remaining hydrogens on the cyclohexane ring and the side-chain carbinol hydrogen give rise to spectral bands which may be analyzed as a five-spin system using standard computer techniques. The nmr chemical shifts and proton–proton coupling constants are found to be consistent with a chair form of the ring in both cis isomers although the isomer with an axial piperidino group appears to have a somewhat flattened ring as a result of steric interactions. Differential line-broadening effects of HD couplings on ring protons in the axial *vs.* equatorial position proved to be useful in making spectral assignments and determining conformational features of the cyclohexane ring.

In an earlier paper,[1] Szmuszkovicz and Skaletzky reported the synthesis and stereochemical analysis of the four racemates of 2-piperidino-α-(p-methoxyphenyl)cyclohexanemethanol (I). The relative con-

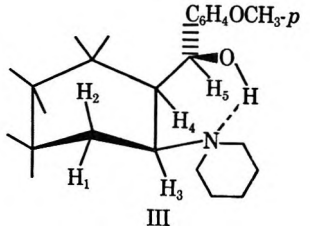


I

figuration and conformation of three of these alcohols were established in detail by means of various chemical transformations and spectroscopic techniques. However, in the cis-substituted cyclohexane with threo configuration of the side chain with respect to adjacent carbon (designated hereafter as *cis*-A), the conformation of the cyclohexane ring may be either a chair with an axial piperidine (II) or a twist-boat with piperidine pseudoequatorial (III). Both II and III are consistent



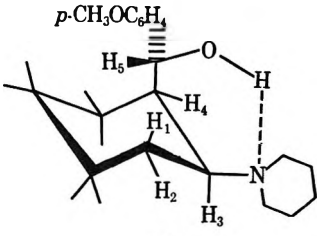
II



III

with the observed data which suggest a molecule with fixed conformation due to intramolecular hydrogen bonding.[2] However, each structure exhibits certain unfavorable steric features that detract from the stabilizing effect of the internal hydrogen bond. The strain associated with an axial piperidine in II is expected to be considerable. While structure III permits this bulky substituent to assume a pseudoequatorial position, the cyclohexane ring takes a less advantageous skew conformation and the large groups attached to the ring tend to eclipse one another. As the evidence presented in ref 1 is in agreement with either II or III and there is some difficulty in accurately estimating the relative steric repulsions in the two systems, the present work was undertaken to investigate the cyclohexane ring conformation using more intensive nmr techniques.

Structure IV was suggested in ref 1 as the probable



IV

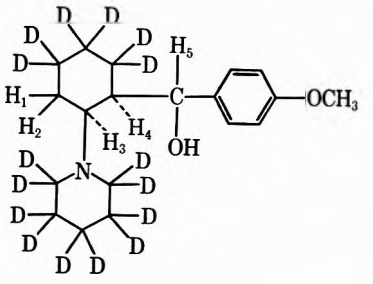
conformation of the cis isomer (*cis*-B) with erythro configuration. The ir and nmr spectra of this compound exhibit features which indicate that intramolecular hydrogen bonding imposes conformational stability in the system. Although there is a large axial substituent on the cyclohexane ring in IV which appears rather disadvantageous, steric interference between the p-methoxyphenyl and cyclohexane ring hydrogens is not serious. In addition, the equatorial orientation of the piperidine ring contributes greatly to the stability of the structure. For these reasons the conclusions of Szmuszkovicz and Skaletzky regarding the geometry of *cis*-B are not con-

(1) J. Szmuszkovicz and L. L. Skaletzky, *J. Org. Chem.*, **32**, 3300 (1967); see also L. L. Skaletzky, B. E. Graham, and J. Szmuszkovicz, *J. Med. Chem.*, **12**, 977 (1969).

(2) In the nmr spectrum of the compound in $CDCl_3$ solution, the OH peak is highly deshielded (δ 7.3-ppm downfield from TMS). Furthermore, infrared measurements in carbon disulfide show hydrogen-bonded hydroxyl down to infinite dilution. Thus, it may be concluded that the hydroxyl is intramolecularly hydrogen bonded to the piperidine nitrogen. Additional nmr evidence for an immobile molecular system is provided by the resonance signal of the carbinol proton (>CH*–OH) which appears as a broad singlet in the 60-MHz spectrum of the alcohol. Since this indicates negligible coupling with the vicinal proton on the cyclohexane ring, a fixed dihedral angle of approximately 90° is predicted. Models II and III are both in accord with these observations (see ref 1 for more complete discussion).

sidered to be in doubt. However, further nmr analysis of this molecule is felt to be desirable for purposes of comparison with the results for *cis*-A.

A complete interpretation of the nmr spectrum, yielding the chemical shifts and coupling constants of all protons, would be desirable to minimize the likelihood of error in making correlations with structural features of the molecule. Unfortunately, hydrogens in the cyclohexane and piperidine rings of I give rise to broad overlapping bands which reveal little detailed line structure. Hence, there is no way to make a full analysis using presently available techniques. Since selective deuteration[3-8] has been used successfully in the past to simplify spectra by eliminating masking signals of protons of lesser interest, model compounds (V) of the two cis piperidino alcohols were synthesized in which 16 of the 20 hydrogens in the cyclohexane and piperidine rings are replaced by deuterium. In each



V

compound, the four remaining hydrogens in the cyclohexane ring and the carbinol hydrogen in the side chain give rise to spectral bands which may be analyzed as a five-spin system using standard computer techniques.[9] Although the existence of HD couplings is a potential source of complication in the proton resonance patterns, the small magnitude of such interactions often leads to little more than apparent line broadening so that adverse effects are minimal.[10] It should be noted that the effects of the HD couplings may provide useful information pertaining to the geometry of the system.

Spectral Analysis.—The regions of interest in the 100-MHz spectra of *cis*-A and *cis*-B are shown in the upper traces of Figures 1 and 2, respectively. In both spectra the signal of the carbinol proton (H_5 in structure V) appears as a doublet approximately 5-ppm downfield from the TMS reference. Since the multiplet at δ 2.95 in Figure 1 appears in a position characteristic of an alkyl CH group bonded to an amine nitrogen, it can be ascribed to H_3. The remaining bands in the two spectra cannot be assigned with confidence by direct inspection. Hence, spin decoupling experiments were utilized to determine the assignments of the upfield signals. For example, in the spectrum of *cis*-A, irradiation of H_5 at 5.0 causes the multiplet at 1.56 to collapse into a broad doublet, thus indicating the position of H_4. A similar experiment with *cis*-B reveals that the pattern centered at 2.27 corresponds to H_4. With this information, the six-peak multiplet at 2.49 in Figure 2 can be assigned to H_3. The geminal hydrogens, H_1 and H_2, give rise to the remaining signals in the two spectra. A sizable chemical shift difference between H_1 and H_2 is evident in the curve for *cis*-A, but the difference is much less in the spectrum of *cis*-B.

Using approximate chemical shifts and coupling constants obtained by inspection as initial data, a series of calculations were performed with the LAOCN3[11] computer program in order to produce refined values. After each computation, a plot of the theoretical spectrum was compared to the experimental curve and appropriate changes in the shifts, couplings, and line widths were made to improve the fit. Although HD couplings were not explicitly included in the calculations, adjustment of line widths compensated to a large extent for the observed effects of such interactions on the spectral bands of H_1, H_2, and H_4. Since some of the HD splittings are partially resolved, a few slight discrepancies between the observed and calculated band shapes may be noted in Figures 1 and 2. However, the overall agreement is quite good. A list of the final nmr parameters for the two molecules is given in Table I.

TABLE I

PROTON MAGNETIC RESONANCE DATA

Hydrogens	Chemical shifts[a]	Apparent line widths[b]	Coupling constants[c,d]
		cis-A	
H_1	2.09	1.3	$J_{12} = -14.8$
			$J_{13} = 2.0$
H_2	1.40	3.0	$J_{23} = 5.7$
H_3	2.95	0.9	$J_{34} = 4.8$
H_4	1.56	2.3	$J_{45} = 2.0$
H_5	5.00	2.0	
		cis-B	
H_1	1.76	3.4	$J_{12} = -12.2$
			$J_{13} = 12.3$
H_2	1.91	2.0	$J_{23} = 3.5$
			$J_{24} = 1.0$
H_3	2.49	1.6	$J_{34} = 3.6$
H_4	2.27	2.0	$J_{45} = 10.0$
H_5	4.98	1.8	

[a] Measured in parts per million (ppm) downfield from TMS. The estimated error in the values is ±0.01 ppm. [b] The values given are the theoretical line widths at half height (measured in hertz) which yield the best visual agreement with observed peak intensities. [c] Measured in hertz with an estimated error of ±0.1 Hz. [d] In compound *cis*-A, the relative signs of J_{12}, J_{13}, and J_{23} were established by the spin tickling method of Friedman and Gutowsky [*J. Chem. Phys.*, **45**, 3158 (1966)]. The geminal coupling was assumed to be negative in accordance with previous studies of saturated alkanes (see J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy." Vol. 2, Pergamon Press, New York, N. Y., 1966, pp 677–683). Generally accepted signs were chosen for compound *cis*-B.

Discussion

Successful correlations between proton–proton coupling constants, $J^{vic}_{HH'}$, in the system HCC'H' and

(3) F. A. L. Anet, *J. Amer. Chem. Soc.*, **84**, 1053 (1962).
(4) A. H. Lewin and S. Winstein, *ibid.*, **84**, 2464 (1962).
(5) A. C. Huitric, J. B. Carr, W. F. Trager, and B. J. Nist, *Tetrahedron*, **19**, 2145 (1963).
(6) F. A. L. Anet, M. Ahmad, and L. D. Hall, *Proc. Chem. Soc., London*, 145 (1964).
(7) E. Premuzic and L. W. Reeves, *J. Chem. Soc. (London)*, 4817 (1964).
(8) E. W. Garbisch, Jr., and M. G. Griffith, *J. Amer. Chem. Soc.*, **90**, 6543 (1968).
(9) J. D. Swalen, *Progr. Nucl. Magn. Resonance Spectrosc.*, **1**, 205 (1966).
(10) Although the effects of HD couplings may be removed by double irradiation, this technique was not employed in the present case because of a lack of the necessary heteronuclear decoupling equipment.
(11) S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, **41**, 3863 (1964); LAOCN3, Mellon Institute, Pittsburgh, Pa., 1966.

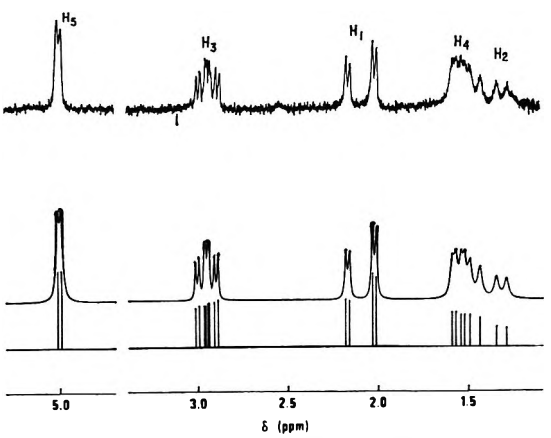


Figure 1.—Upper trace: 100-MHz spectrum of partially deuterated *cis*-A in 0.01 *M* $CDCl_3$ solution. Lower trace: plot of calculated spectrum with adjusted line widths to compensate for broadening effects of HD interactions.

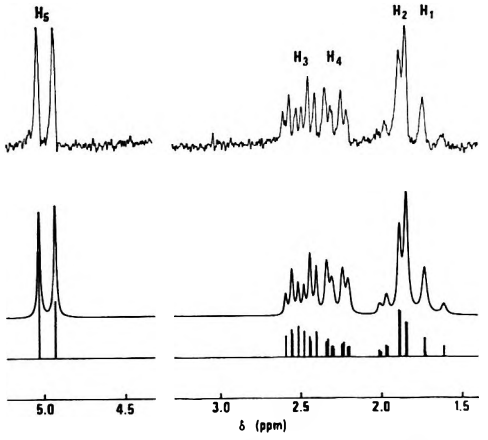


Figure 2.—Upper trace: time-averaged 100-MHz spectrum of partially deuterated *cis*-B in 0.001 *M* $CDCl_3$ solution. The spectrum was drawn after 265 scans on the Varian C-1024 CAT. Lower trace: plot of calculated spectrum with adjusted line widths to compensate for effects of HD couplings.

dihedral angles, $\phi_{HH'}$, have often been made using relationships of the form[12]

$$J^{vic}_{HH'} = A \cos^2 \phi_{HH'} + B \cos \phi_{HH'} \quad (1)$$

where the coefficients A and B depend upon the CC separation, the CCH bond angles, and the ionic effects of other substituents on the carbons.[13] Relative differences in bond lengths and bond angles in the cyclohexane rings of the two cis isomers under consideration are expected to be minimal on account of the constraints of the cyclic system. However, previous studies[14-16] have indicated that changing the positions of bulky ring substituents does alter the ring geometry somewhat causing differences in the coefficients A and B of eq 1. The resultant uncertainty in predicting dihedral angles from observed vicinal couplings is roughly ±20%. Nevertheless, eq 1 provides a useful basis from which to draw qualitative conclusions regarding ring geometry. For the purpose of making order-of-magnitude comparisons, consider the relationship with A = 13 Hz and B = 0 which are similar to the coefficients given by Garbisch and Griffith[8] for cyclohexane. If distortions of the ring from a perfect chair form are neglected, we obtain the following possible vicinal coupling constants between protons in various ring configurations: J_{aa} = 13 Hz and $J_{ae} = J_{ee}$ = 3.2 Hz. For a perfect boat form, the vicinal proton–proton couplings are $J_{aa'} = J_{a'a'} = J_{e'e'}$ = 13 Hz and $J_{ae'} = J_{ae} = J_{ee'} = J_{a'e'}$ = 3.2 Hz, where a denotes the flag hydrogen, e the bowsprit, a′ indicates a pseudoaxial hydrogen, and e′ a pseudoequatorial hydrogen. Although the eclipsed interactions associated with the boat form make this conformation highly unlikely, some twisting of the ring would reduce the repulsions considerably. The flexible nature of the boat form allows such skewing without undue distortion of bond lengths and angles in the ring. Variations in the vicinal coupling constants due to deviations of the dihedral angles from those of a perfect boat conformation may be predicted qualitatively using eq 1.

(12) M. Barfield and D. M. Grant, *Advan. Magn. Resonance*, **1**, 149 (1965).
(13) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).
(14) R. U. Lemieux and J. W. Lown, *Tetrahedron Lett.*, 1229 (1963).
(15) F. A. L. Anet, R. A. B. Bannard, and L. O. Hall, *Can. J. Chem.*, **41**, 2331 (1963).
(16) F. A. L. Anet, *J. Amer. Chem. Soc.*, **84**, 1053 (1962).

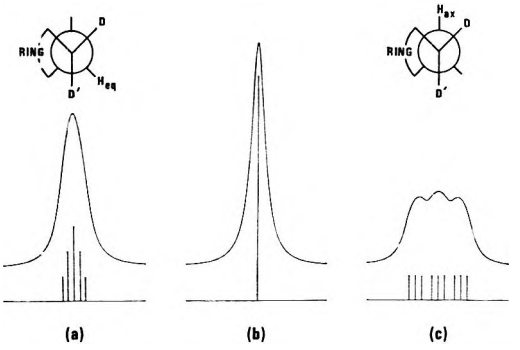


Figure 3.—Schematic representations of first-order perturbing effects of an adjacent CD_2 group on a proton spectral line when (a) H is equatorial in the cyclohexane ring, (b) the HD interactions are decoupled by irradiating the deuterium nuclei, and (c) H is axial.

The effects of the vicinal proton–deuterium coupling constants also provide a source of conformational data. It is possible to estimate the magnitude of J^{vic}_{HD} from the coupling $J^{vic}_{HH'}$ in the corresponding system where H′ replaces D by using the expression

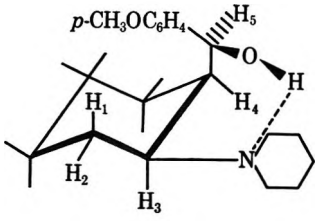
$$J^{vic}_{HD} = \frac{\gamma_D}{\gamma_H} J^{vic}_{HH'} = 0.1535\, J^{vic}_{HH'} \quad (2)$$

where γ_D and γ_H are the respective magnetogyric ratios of the isotopes. As γ_D is less than one-sixth of γ_H, the splittings due to vicinal deuterium atoms in a saturated molecule generally will be no more than 2 Hz. This fact, combined with complex resonance patterns resulting from the deuterium magnetic quantum number I_D = 1, often leads to unresolved splittings and apparent line broadening in the proton spectrum. As shown in the schematic drawings of Figure 3, the effect of an adjacent CD_2 group on the spectral lines of a given hydrogen depends greatly on the position of the hydrogen. Although the HD couplings lead to significant line broadening when H is equatorial, an even wider pattern with some resolution of the component lines may result if H is axial. The apparent line widths of H_1, H_2, and H_4 in the partially deuterated cis piperidino alcohols clearly show these effects.

It is of interest to examine the experimental nmr data for compound *cis*-B in light of the foregoing observations H_3 experiences one large axial–axial cou-

pling and two smaller axial–equatorial interactions in accord with the requirements of structure IV. Furthermore, the signals corresponding to the axial H_1 are ~1.4-Hz wider than those of the equatorial hydrogens, H_2 and H_4. The signals of H_3 and H_5, which experience no significant HD coupling, are much narrower as expected. An interesting item is the existence of long-range coupling between the equatorial hydrogens H_2 and H_4 in agreement with previous observations on various saturated six-membered-ring compounds.[17] The observed value of J_{45} is also consistent with IV in that it could correspond to a dihedral angle $\phi_{45} \approx 150°$, thus facilitating formation of an internal hydrogen bond between the hydroxyl group and the piperidino nitrogen.

The vicinal couplings exhibited by H_3 in compound *cis*-A do not agree well with the theoretical values for either a perfect chair or a boat conformation of the cyclohexane ring. A possible explanation for the disagreement could be the existence of an equilibrium between II and its inverted isomer VI. However, there



VI

is an axial–axial relationship between H_1 and H_3 in VI which would contribute a sizable amount to the observed value of J_{13} if this isomer were present to a significant degree. Since the actual value of J_{13} is much too small in *cis*-A to allow for any contribution from VI, it is concluded that the presence of this structure may be discounted.[18] As the foregoing explanation for the disagreement must be discarded, it might be argued that the assumed magnitudes of the terms A and B used in eq 1 to obtain the theoretical couplings are exceptionally poor for this case. However, the relation yields satisfactory correlations for compound *cis*-B and severe distortions of the cyclohexane ring in *cis*-A would be required to alter the values of A and B sufficiently to produce the observed shifts. Hence, it is felt that the coupling constants mainly reflect changes in the dihedral angles resulting from a slight cyclohexane ring deformation.

One possibility that may be ruled out is a twist–boat conformation similar to that of structure III with H_1 as bowsprit, H_2 in the flag position, and the remaining ring hydrogens, H_3 and H_4, in pseudoaxial positions. The fact that J_{23} and J_{34} are larger than J_{13} is consistent with this assignment. In order to obtain theoretical couplings of the magnitude observed, eq 1 requires dihedral angles of the order $\phi_{13} \approx 70°$, $\phi_{23} \approx 130°$, and $\phi_{34} \approx 50°$. However, these angles are not mutually compatible since pseudorotation of the boat in a direction which yields qualitatively correct values for ϕ_{23} and ϕ_{34} simultaneously gives $\phi_{13} \approx 10°$ ($J_{13} \approx 12.7$ Hz). Furthermore, the pseudorotation would almost restore the ring to a perfect boat with the piperidino group in pseudoaxial position which is indeed a highly unfavorable arrangement. As a second possibility, the cyclohexane ring could assume a slightly distorted chair conformation appearing much like structure II. With this arrangement H_1 and H_3 are designated as equatorial hydrogens while H_2 and H_4 are assigned to axial positions. In this case, the approximate dihedral angles predicted by eq 1 would be $\phi_{13} \approx 70°$, $\phi_{23} \approx 50°$, and $\phi_{34} \approx 50°$. These angles correspond well with the results expected for a flattened chair in which the stress associated with an axial piperidino group has been relieved somewhat by tipping the group away from the ring center. The value of J_{45} does not appear to be of consequence in deciding between the two possible *cis*-A structures. It corresponds to a dihedral angle, $\phi_{45} \approx 70°$, which permits formation of an internal hydrogen bond in both cases.

A summary of the conclusions drawn from the vicinal coupling data is given in Table II. Omitted from the table are those sets of dihedral angles which correspond to boat forms of the cyclohexane ring with bulky substituents in flag or pseudoaxial positions. Such structures are considered highly unlikely on steric grounds. Although the vicinal proton–proton coupling constants seem to be in accord with a flattened chair conformation for the *cis*-A ring, the approximate nature of the correlation makes it imperative to investigate the remaining nmr data for corroborative or contradictory evidence.

TABLE II

RELATIONSHIPS BETWEEN VICINAL COUPLING CONSTANTS AND MOLECULAR GEOMETRY IN *cis*-A AND *cis*-B

Compd	H,H′	$J^{vic}_{HH'}$, Hz	$\phi_{HH'}$,[a] degrees	Configuration	Suggested cyclohexane ring conformation
cis-A	H_1,H_3	2.0	70	ee	
	H_2,H_3	5.7	50	ae	Slightly flattened chair
	H_3,H_4	4.8	50	ea	
	H_4,H_5	2.0	70	Gauche	
cis-B	H_1,H_3	12.3	170	aa	
	H_2,H_3	3.5	60	ea	Chair
	H_3,H_4	3.6	60	ae	
	H_4,H_5	10.0	150	Trans	

[a] In accordance with the approximate nature of eq 1, the dihedral angles are given to the nearest 10° for the purpose of indicating orders of magnitude. Although there are two possible angles for each coupling, only those combinations consistent with the geometric requirements of cyclohexane ring are reported.

In compound *cis*-A, the signals of H_1, H_2, and H_4 display the expected line-broadening effects of HD coupling. The relative line widths are also consistent with the assigned configurations of the three hydrogens in the deformed chair structure. It is interesting to note that the line widths in the H_2 multiplet are considerably broader than the lines of the other axial hydrogen H_4 while the equatorial H_1 signals are surprisingly narrow. These data suggest that the HD dihedral angles are reflecting the changes associated with flattening of the cyclohexane ring.

According to Pople and Bothner-By,[19] the magnitude of the geminal coupling constant in a methylene group is sensitive to the relative configuration of an electronegative substituent, X, on an adjacent carbon. The

(17) A. Rassat, C. W. Jefford, J. M. Lehn, and B. Waegell, *Tetrahedron Lett.*, No. 5, 233 (1964).

(18) This is in agreement with the conclusions given in ref 1 which eliminated structure VI on the basis of severe steric interactions between the aromatic and cyclohexane rings.

(19) J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.*, **42**, 1339 (1965).

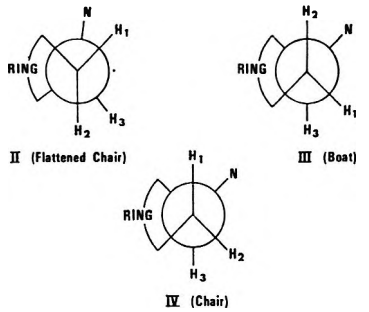


Figure 4.—Relative configurations of H_1, H_2, H_3, and N in structures II, III, and IV. The projection view in each case is down the bond connecting the carbon on which H_1 and H_2 are located with the carbon to which H_3 and the piperidino group are attached.

theory predicts an algebraic decrease in J_{HH}^{gem} when the electron-withdrawing atom or group is trans to one of the CH_2 hydrogens. If both hydrogens are gauche to X, a small positive contribution to the geminal coupling is expected. It is, therefore, possible to qualitatively account for the observed 2.5-Hz difference in J_{12} between compounds *cis*-A and *cis*-B on the basis of the relative configurations of H_1, H_2, and the piperidino nitrogen. The diagrams of Figure 4 show that H_1 and H_2 are both gauche to N in structures III and IV. Hence, if *cis*-A were similar to III, the experimental value for J_{12} would be expected to differ negligibly from the corresponding coupling in *cis*-B. It is noted that H_2 and N would be nearly trans in the flattened chair. As this would give rise to a negative contribution to J_{12}, the observed difference in the geminal couplings follows from the theory and gives additional support to the proposal that *cis*-A has structure II.[20]

In the absence of shielding effects from sources external to the cyclohexane ring, it has been found that axial hydrogens exhibit resonance signals approximately 0.5-ppm upfield from equatorial hydrogens if the ring adopts the chair form and does not undergo rapid conformational interconversion.[21] With substituted cyclohexanes, the relative shifts of the ring hydrogens may be greatly altered or even reversed by the magnetic shielding effects of the attached groups. In both *cis*-A and *cis*-B, the ring substituents should give rise to significant shifts as a result of electronegativity differences, magnetic anisotropy, and steric interactions. In order to determine whether the chemical shifts of ring hydrogens in *cis*-A exhibit unusual features not in accord with the proposed structure II, the resonance position of each hydrogen may be compared with that of its identically numbered, but oppositely oriented, counterpart in *cis*-B. The resulting chemical shift differences listed in Table III demonstrate in every case that the equatorial hydrogen resonates at lower field than the corresponding axial hydrogen. However, the wide variation in the quantity $\delta_e-\delta_a$ indicates that the ring substituents do exert significant long-range shielding effects in the two compounds. Nevertheless, the observed chemical shifts are quite compatible with the proposed structure II for compound *cis*-A.

(20) Widening of the C–CH_2–C angle in the cyclohexane ring also yields a negative contribution to J_{12} [see R. Cahill, R. C. Cookson, and T. A. Crabb, *Tetrahedron*, **25**, 4711 (1969)]. A slight widening of this angle should accompany flattening of the cyclohexane ring.

(21) F. A. Bovey, F. P. Hood, E. W. Anderson, and R. L. Kornegay, *Proc. Chem. Soc.*, 418 (1964).

TABLE III

COMPARISON OF CHEMICAL SHIFTS EXHIBITED BY CORRESPONDING RING HYDROGENS IN *cis*-A AND *cis*-B

Hydrogen	Ring configuration II	Ring configuration IV	$\delta_e-\delta_a$, ppm
H_1	e	a	0.33
H_2	a	e	0.51
H_3	e	a	0.46
H_4	a	e	0.71

In summary, analysis of the nmr data obtained from the selectively deuterated cis 1,3-piperidino alcohols (V) leads to the conclusion that the cyclohexane ring possesses a chair conformation in both isomers. The evidence best fits a slightly flattened chair for compound *cis*-A in which the bulky piperidino group assumes an axial position.[22]

Experimental Section

The synthesis of the deuterated *cis*-A and *cis*-B isomers V was based on the previously described preparation of this class of compound.[1]

2-(*p*-Methoxybenzoyl)cyclohexanone-3,3,4,4,5,5-d_6.—Cyclohexanone-3,3,4,4,5,5-d_6 was synthesized from cyclohexanone-d_{10} (Merck and Co.) in a manner analogous to that described by Anet[23] for the preparation of cyclohexanone-2,2,6,6-d_4. The presence of a molecular ion at m/e 104 confirmed the isotopic composition.

The pyrrolidine enamine of cyclohexanone-3,3,4,4,5,5-d_6 was prepared from 0.5 g (0.0048 mol) of cyclohexanone-3,3,4,4,5,5-d_6 and 2 g of distilled pyrrolidine in 100 ml of dry benzene at reflux for 2 hr using a Soxhlet with an extraction thimble containing 10 g of Linde Molecular Sieves No. 4A. The benzene was evaporated and the oil residue dissolved in 16 ml of chloroform (purified by passage through Woelm neutral alumina, activity I).

A solution of 0.86 g (0.00504 mol) of *p*-anisoyl chloride in 1 ml of purified chloroform was added over 4 min to the above chloroform solution and 0.5 g (0.00495 mol) of distilled triethylamine in a nitrogen atmosphere at 0–5°. The reaction was stirred for 1 hr at 0–10° and then for 16 hr at room temperature. Work-up in the usual way gave 0.439 g (38.5%) of the keto–enol forms, mp 64–80°. In a subsequent run the yield of product was 49%. The mass spectrum showed a molecular ion at 238 (calcd 238).

***cis*-A-(2-Piperidino)-α-(*p*-methoxyphenyl)cyclohexanemethanol-d_{16}.**—Piperidine-d_{10} (NH) was prepared by equilibration of 0.500 g of piperidine-d_{11} (Merck and Co.) with 0.5 ml of water and 5 mg of *p*-toluenesulfonic acid monohydrate in toluene in a stoppered round-bottomed flask. The toluene layer was dried by stirring over 3 g of Linde Molecular Sieves No. 4A for 30 min. This drying procedure was repeated with 3 g of fresh molecular sieves. The toluene layer was combined with toluene washings of the molecular sieves and filtered (gravity) into a 30-ml round-bottomed flask fitted with a 10-ml-capacity Soxhlet and an extraction thimble containing 1.5 g of fresh molecular sieves.

To the toluene solution was added 10 mg of *p*-toluenesulfonic acid monohydrate and 0.238 g (0.001 mol) of 2-(*p*-methoxybenzoyl)cyclohexanone-3,3,4,4,5,5-d_6; the solution was heated at reflux under nitrogen for 16 hr. The toluene was evaporated *in vacuo*. The enamine was dissolved in 25 ml of dry ethanol and hydrogenated in the presence of 0.10 g of platinum oxide for 21 hr at an initial pressure of 50 psi. The solvent was evaporated and the residue dissolved in 15 ml of ether which was extracted with five 5-ml portions of 10% acetic acid. The acetic acid layer was cooled and then basified with 20% sodium hydroxide. The resulting oil was extracted into ether and the dried ether layer evaporated to 0.26 g of oil. The hydrochloride was prepared and crystallized from methanol–ether, 0.242 g (68%), mp 238–238.5°.

(22) It is of interest to note that in the case of the hydrochloride of *cis*-A (V HCl) in D_2O where intramolecular hydrogen bonding may play a minor role, nmr analysis indicates that the piperidino group adopts the more stable equatorial position.

(23) F. A. L Anet, *Can. J. Chem.*, **39**, 2262 (1961).

The mass spectrum indicated d_{16} (m/e 319) and a minor quantity of d_{15} (m/e 318). A sample of the hydrochloride was converted to the free base and purified by silica gel chromatography eluting with methanol–methylene chloride mixtures.

cis-B, 2-Piperidino-α-(*p*-methoxyphenyl)cyclohexanemethanol-d_{16}.—A sample of *cis*-A free base was isomerized with trifluoroacetic acid as previously described.[1] The crude product was purified by silica gel chromatography and crystallization from ether (−20°), mp 133–135°. The mass spectrum was the same as the spectrum of the *cis*-A isomer.

Registry No.—*cis*-A, 13724-43-1; *cis*-B, 13724-46-4.

A Synthesis of Dihydrothiopyran-3-ones. The Intramolecular Cyclization of Allylthioglycolic Acid Chlorides

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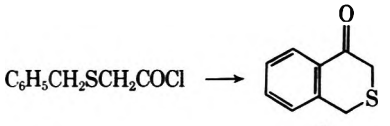
Intramolecular cyclization of allylthioglycolic acid chloride effected by aluminum chloride gave two products, 3,4-dihydro-2*H*-thiopyran-3-one and 3,6-dihydro-2*H*-thiopyran-3-one. Under similar conditions 3-methyl-, 2-methyl-, and 3,3-dimethylallylthioglycolic acid chloride produced 4-methyl- and 5-methyl-3,6-dihydro-2*H*-thiopyran-3-one and 4-isopropylidenetetrahydrothiophen-3-one, respectively. The substituent effects on the directionality of cyclization are discussed.

While the chemistry of thiopyrones have been widely investigated, little is known about the synthesis and chemical behavior of the isomeric thiopyran-3-one system. In the course of our study on the intramolecular cyclization of compounds containing heteroatoms, we are interested in thiopyran-3-ones, and we have now developed a novel and versatile synthesis for 3,6-dihydrothiopyran-3-ones bearing substituents on the ring.

The cyclization of benzylthioglycolic acid chloride reportedly produces isothiochromanone-4 (**1**).[1] Analogous formation of the parent thiopyranone **2** has not



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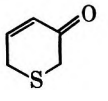
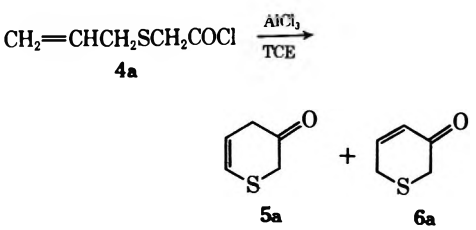


2

been reported.[2] We report here successful cyclization of allythioglycolic acid chlorides to the previously unknown thiopyranone.

Allylthioglycolic acid (**3a**)[3] was synthesized in 82% yield by the reaction of allyl chloride with thioglycolic acid in aqueous sodium hydroxide solution. The acid was then converted into the acid chloride **4a** in 89% yield by the reaction with thionyl chloride. Treatment of acid chloride **4a** with aluminum chloride in 1,1,2,2-tetrachloroethane (TCE) at 50–55° gave **5a** and **6a** in a ratio of 53:47.

The structure of the lower boiling compound **5a**, 3,4-dihydro-2*H*-thiopyran-3-one, was suggested by a combination of spectral data: ir 1710, 960, and 655 cm^{-1}; uv 221 and 242 mμ (α,β-unsaturated sulfide); nmr two methylene groups at δ 3.23 and 2.97 ppm, and

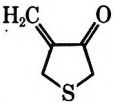


4a **5a** **6a**

two olefinic protons at δ 5.83 and 6.25 ppm (each double triplet).

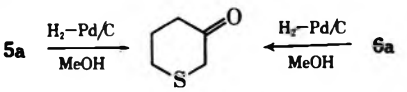
Another higher boiling product **6a**, 3,6-dihydro-2*H*-thiopyran-3-one, was characterized by a carbonyl band at 1670 cm^{-1} and uv absorption maximum at 234 mμ, suggesting the presence of a CH=CHCO unit. The nmr spectrum of **6a** showed signals of two olefinic protons at δ 5.89 and 6.90 ppm (each double triplet), as well as two methylene groups at δ 3.20 and 3.21 ppm.

Cyclization of **4a** would be expected to lead to 3,6-dihydro-2*H*-thiopyran-3-one (**6a**), to 3,4-dihydro-2*H*-thiopyran-3-one (**5a**), or to 4-methylenetetrahydrothiophen-3-one (**7a**). The third possible product **7a** was



7a

not formed, since the ir spectra of products, especially that of the higher boiling material having a conjugated carbonyl function, showed no absorption of a methylene group at *ca.* 890 cm^{-1} or somewhat higher region,[4] and nmr pattern of olefinic proton signals of products is characteristic as a cis-disubstituted olefin rather than a exo methylene system (**7a**). The assignment of a thiopyran-3-one skeleton to our products was ultimately confirmed by catalytic reduction of **5a** and **6a** to the known ketone **8**.[5]



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(1) (a) R. Lesser and A. Mehrländer, *Ber.*, *B*, **56**, 1642 (1932); (b) P. Cagniant and M. P. Cagniant, *Bull. Soc. Chim. Fr.*, 1998 (1959).

(2) Quite recently W. C. Lumma, Jr., and G. A. Berchtold [*J. Org. Chem.*, **34**, 1566 (1969)] have independently reported the synthesis and photochemistry of 5-methyl-3,6-dihydro-2*H*-thiopyran-3-one.

(3) (a) E. Larsson and B. O. Osberg, *Acta Chem. Scand.*, **14**, 768 (1960); (b) E. Larsson, *Ber.*, **63**, 1347 (1930).

(4) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 51.

(5) (a) N. J. Leonard and J. Figueras, Jr., *J. Amer. Chem. Soc.*, **74**, 917 (1952); (b) E. A. Fehnel, *ibid.*, **74**, 1569 (1952).

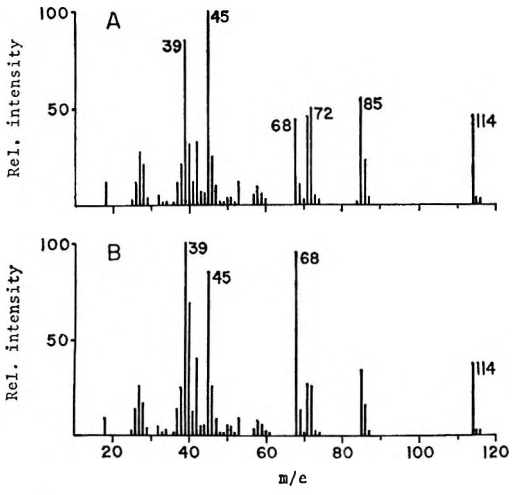
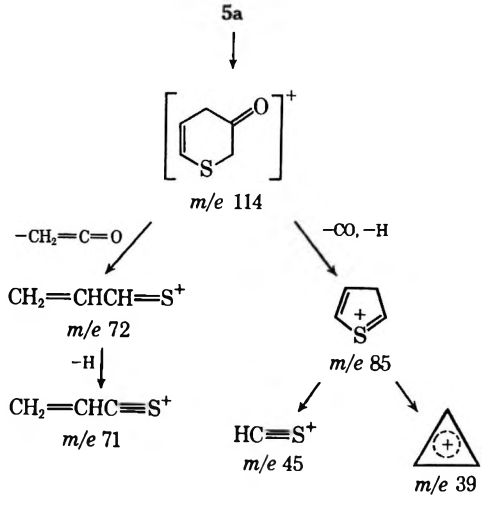


Figure 1.—Mass spectra of (A) **5a** and (B) **6a**.

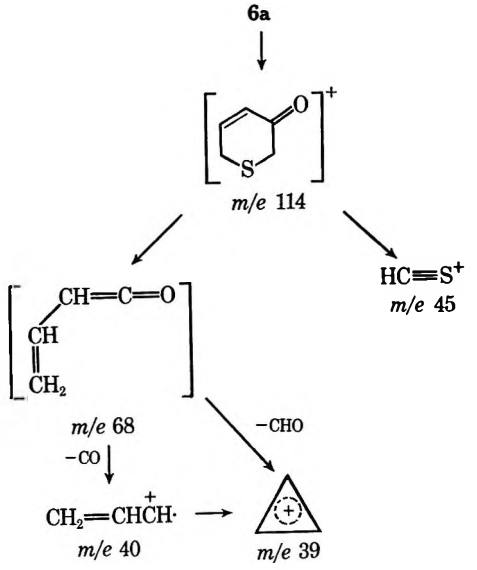
The position of the double bonds of **5a** and **6a** was additionally confirmed on the basis of mass spectral fragmentation pattern (Figure 1). Although both mass spectra of **5a** and **6a** indicate almost identical fragmentation, careful examination of relative intensity suggests that the structural assignment of $\Delta^{5,6}$-dihydrothiopyran-3-one and $\Delta^{4,5}$-dihydrothiopyran-3-one to **5a** and **6a**, respectively, is correct. Thus, the relatively intense peak of *m/e* 85 in the spectrum of **5a** compared to that of **6a** is caused by elimination of a molecule of CHO from the molecular ion to form a five-membered $C_4H_5S^+$ ion (85) which then degrades to the well-stabilized $HC{\equiv}S^+$ ion (45) and cyclopropenyl cation $C_3H_3^+$ (39). Two fragment ion peaks of *m/e* 72 ($C_3H_4S^+$) and 71 ($C_3H_3S^+$) seem to be produced by the elimination of ketene from **5a** by a retro-Diels-Alder fission (Scheme I).

SCHEME I
POSSIBLE FRAGMENTATION PATH OF 5a



On the other hand, the main degradation path of **6a** is explained by bond fission between C-2 and C-3 and between C-6 and S, forming possibly vinylketene ion $C_4H_4O^+$ (68) and $HC{\equiv}S^+$. Further degradation of the former ion leads, with expulsion of CO, to allene ion (40) or, with lose of HCO, to the cyclopropenyl cation (Scheme II).

SCHEME II
POSSIBLE FRAGMENTATION PATH OF 6a



Two strong peaks of $HC{\equiv}S^+$ (45) and $C_3H_3^+$ (39) which are frequently observed in the mass spectrum of sulfur-containing heterocyclic compounds,[6] may also be produced by a direct fission of **5a** and **6a**.

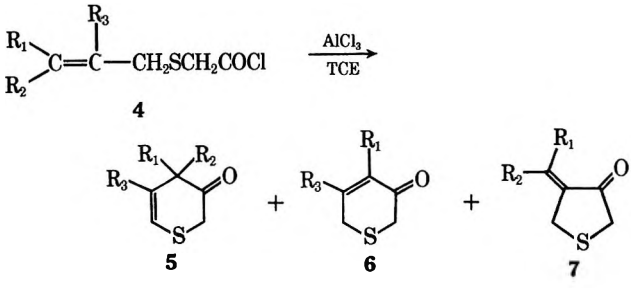
In order to examine the ratio of formation of **5a** and **6a**, a brief study of the influence of catalyst and solvent on the cyclization of **4a** was made, the results of which are summarized in Table I. In each case studied, 3,4-dihydro-2*H*-thiopyran-3-one was obtained in preferential amount.

TABLE I
CYCLIZATION OF 4a IN VARIOUS CONDITIONS

Solvent	Catalyst	Temp, °C	Time, hr	Yield, %	Ratio, 5a:6a
CS_2	$AlCl_3$	Reflux	4.5	23	65:35
TCE[a]	$AlCl_3$	50–55	4.0	42	53:47
TCE	$AlCl_3$	55–65	3.5	22	70:30
CS_2	$SnCl_4$	28–30	3.5	22	100:0
CS_2	$BF_3 \cdot OEt_2$	Reflux	2.5	0	

[a] 1,1,2,2-Tetrachloroethane.

Cyclization of Substituted Allylthioglycolic Acid Chlorides.—The cyclization of allylthioglycolic acid chloride (**4a**) to give exclusively two isomeric six-membered cyclenones **5a** and **6a** without formation of any



a, $R_1 = H$; $R_2 = H$; $R_3 = H$
b, $R_1 = CH_3$; $R_2 = H$; $R_3 = H$
c, $R_1 = H$; $R_2 = H$; $R_3 = CH_3$
d, $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = H$
e, $R_1 = C_6H_5$; $R_2 = H$; $R_3 = H$

(6) G. Spiteller, *Advan. Heterocycl. Chem.*, **7**, 312 (1966).

five-membered-ring compound prompted us to examine the possible effect of alkyl substitution on the cyclization of the corresponding allylthioglycolic acid chloride. Thus, we have studied the cyclization of 3-methylallyl- (crotyl-), 2-methylallyl- (methallyl-), 3,3-dimethylallyl- (prenyl-), and 3-phenylallyl- (cinnamyl-) thioglycolic acid chlorides (**4b–e**). The acid chlorides **4b–d** were prepared from the corresponding acids **3b–d** with thionyl chloride, but the attempted synthesis of **4e** from cinnamylthioglycolic acid (**3e**) and thionyl chloride under various conditions was unsuccessful. Cyclization was carried out with aluminum chloride at 50–55° in TCE and results are summarized in Table II.

TABLE II

CYCLIZATION OF ALLYLTHIOGLYCOLIC ACID CHLORIDES

Compd	Temp, °C	Time, hr	Products	Yield, %
4a	50–55	4.5	**5a** (53%), **6a** (47%)	42
4b	50–53	2.5	**6b**	30
4c	50–53	2.5	**6c**	49
4d	50–53	1.5	**7d**	21

The structure assignment for the products emerged from an investigation of ir, uv, and nmr spectra.[7] As shown in Table II, the cyclization of **4b** or **4c** afforded single products, the six-membered, conjugated cyclenones **6b** and **6c**, respectively. However, **4d** was converted exclusively to the five-membered-ring ketone **7d**. This abnormal behavior is attributed to the stabilization of the carbonium ion from **4d** by methyl groups and/or the steric requirement of these methyl groups. Since the cyclization of 5-hexenoyl chloride has been reported to lead to 2-cyclohexenone and that of 5-heptenoyl chloride to 2-methyl-2-cyclohexenone,[9] substitution of C-3 methylene function of $\Delta^{5,6}$-unsaturated acid with thia linkage seems to exert no notable influence on the mode of the cyclization of acid chlorides.

Experimental Section

General.—Melting points and boiling points are uncorrected. The infrared spectra were recorded with a Hitachi Model EPI-S2 spectrophotometer and the uv spectra with a Hitachi Model EPS-3T spectrophotometer. The nmr spectra were obtained on a JEOL Model C-60H spectrometer in carbon tetrachloride solution with tetramethylsilane as an internal reference. The mass spectra were determined on a Hitachi Model RMU-6E spectrometer. Gas chromatography was carried out on a Shimadzu Model GC-1C gas chromatograph using a 3 mm × 260 cm column of 25% silicone DC200 on Celite 545 with He as the carrier gas.

Starting Materials.—3-Methylallyl alcohol,[10] 3-methylallyl bromide,[11] 3,3-dimethylallyl bromide,[12] and cinnamyl bromide[13] were prepared by the methods described in the literatures. The other chemicals were commercially available and purified by usual procedures before use.

Allylthioglycolic Acids (3a–e).—These acids were obtained by the modified procedure reported by Larsson and Osberg.[3a] 3-Methylallylthioglycolic acid (**3b**) was prepared in 65% yield: bp 94–98° (0.13 mm); n^{20}D 1.5057; ir 2930 (OH), 1705 (C=O), 960 cm^{-1} (CH=CH). *Anal.* Calcd for $C_6H_{10}O_2S$: C, 49.29; H, 6.89. Found: C, 48.81; H, 7.16.

Allylthioglycolic Acid Chlorides (4a–d).—Allylthioglycolic acid (**3a**) (16.6 g, 0.13 mol) and a large excess of thionyl chloride (30 ml) were refluxed for 1 hr. After removal of the remaining thionyl chloride under reduced pressure, the residual oil was distilled to give 16.8 g of allylthioglycolic acid chloride [**4a**, 89%, bp 63–65° (6 mm)]. Crotylthioglycolic acid chloride (**4b**), methallylthioglycolic acid chloride (**4c**), and prenylthioglycolic acid chloride (**4d**) were similarly prepared, carbon disulfide being used as solvent in the case of **4c** and **4d**. The results are summarized in Table III.

3,4-Dihydro-2*H*-thiopyran-3-one (5a) and 3,6-Dihydro-2*H*-thiopyran-3-one (6a).—A solution of **4a** (15.2 g, 0.10 mol) in dry TCE (40 ml) was slowly added over a period of 3.5 hr to a stirred solution of anhydrous aluminum chloride (15.0 g, 0.11 mol) in dry TCE (80 ml) at 50–55°. Stirring was continued for 1 hr at 50–55°, and then the mixture was cooled and poured into ice and diluted hydrochloric acid. The organic layer was separated and the aqueous layer extracted with ether (four 30-ml portions). The combined organic layer was washed with saturated sodium bicarbonate solution, then saturated sodium chloride solution, and dried (Na_2SO_4). After the evaporation of solvent *in vacuo*, distillation of the dark residue gave a light yellow oil (4.8 g, yield 42%), bp 70–80° (12 mm). Gas chromatographic analysis at 150° and 30 ml/min He flow showed two peaks with retention times 3.1 (53%) and 4.2 min (47%). The products were separated by preparative gas chromatography over silicone DC200. Redistillation of the former gave **5a** as a colorless oil: bp 64–68° (5 mm); n^{20}D 1.5571; ir 1710 (C=O), 1390, 1238, 960 (CH=CH), 750, 655 cm^{-1}; uv λ_{max} (95% EtOH) 221 mμ (ε 3540), 242 (3140), 374 (94); nmr δ 2.97 (m, 2 H), 3.23 (s, 2 H), 5.83 (double t, 1 H, J = 9 and 3.7 Hz), 6.25 ppm (double t, J = 9 and 1.2 Hz); mass spectrum m/e (rel intensity) 114 (46), 85 (55), 72 (49), 71 (46), 68 (44), 45 (100), 40 (31), 39 (85), 27 (27). The semicarbazone had mp 164–170° dec (nitromethane).

Anal. Calcd for $C_6H_9ON_3S$ (semicarbazone): C, 42.09; H, 5.30; N, 24.54. Found: C, 41.86; H, 5.40; N, 24.33.

On the other hand, the distillation of the latter gave **6a** as a colorless oil: bp 70–72° (4 mm); n^{20}D 1.5642; ir 1670 (C=O), 1400, 1380, 1250, 875, 750, 695 cm^{-1}; uv λ_{max} (95% EtOH) 234 mμ (ε 6750), 367 (26); nmr δ 3.20 (s, 2 H), 3.21 (m, 2 H), 5.89 (double t, 1 H, J = 10.5 and 1.5 Hz), 6.90 ppm (double t, 1 H, J = 10.5 and 4.05 Hz); mass spectrum m/e (rel intensity) 114 (37), 85 (33), 72 (25), 71 (27), 68 (97), 45 (85), 40 (69), 39 (100), 27 (25).

Tetrahydrothiopyran-3-one (8).—The dihydrothiopyran-3-one **5a** (0.5 g) was hydrogenated in methanol in the presence of 5% Pd/C (1.0 g) at room temperature. Evaporation of the solvent gave **8** (0.2 g) as a colorless liquid: ir 2924, 1710 (C=O), 1228, 760 cm^{-1} (CSC); nmr δ 2.38 (m, 2 H), 2.40 (broad s, 2 H), 2.73 (m, 2 H), 3.09 ppm (s, 2 H); mass spectrum m/e (rel intensity) 116 (100), 61 (33), 60 (96), 55 (33), 46 (71), 42 (71), 41 (33), 39 (41). The semicarbazone had mp 163–164° (aqueous EtOH) (lit. mp 166.5–167°,[5a] 165–166°[5b]).

Olefin **6a** was similarly hydrogenated to give **8** which was identical with that obtained from **5a** by comparison of ir and nmr spectra and the retention time of glpc.

Tetrahydrothiopyran-3-one 1,1-dioxide was obtained as a colorless solid on treatment of **8** with excess 30% hydrogen peroxide in glacial acetic acid–acetic anhydride. Recrystallization of the product from ethanol afforded colorless crystals melting at 147–148° (lit.[6b] mp 140–140.5°). Nmr spectrum in DMSO-d_6 showed multiplets at δ 2.05, 3.42, and 4.30 ppm.

Anal. Calcd for $C_5H_8O_3S$: C, 40.52; H, 5.44. Found: C, 40.67; H, 5.53.

(7) Cyclization of **4b** would be expected to lead to 5-methyl-3,6-dihydro-2*H*-thiopyran-3-one (**6b**) and/or 4-ethylidenetetrahydrothiophen-3-one (**7b**), but the latter formula was eliminated chiefly because of the small coupling constant (1.5 Hz) between the olefinic proton and the methyl protons on the olefin carbon. The coupling constant between these protons of **7b** would fall in the range of 4–10 Hz.[8]

(8) (a) D. J. Pasto and C. R. Johnson, "Organic Structure Determination," Prentice-Hall, Englewood Cliffs, N. J., 1969, p 183; (b) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press, Long Island City, N. Y., 1966, pp 710–745.

(9) (a) M. F. Ansell and S. S. Brown, *J. Chem. Soc.*, 2955 (1958); (b) M. O. Riose, *C. R. Acad. Sci.*, **248**, 2774 (1959).

(10) R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.*, **69**, 1197 (1947).

(11) W. G. Young and J. F. Lane, *ibid.*, **59**, 2051 (1937).

(12) J. Tanaka, T. Katagiri, and S. Yamada, *J. Chem. Soc. Jap.*, **87**, 877 (1966).

(13) P. A. Briscoe, F. Challenger, and P. S. Duckworth, *J. Chem. Soc.*, 1755 (1956).

TABLE III

ALLYLTHIOGLYCOLIC ACID CHLORIDES[a]

Compd	Yield, %	Bp, °C (mm)	$n^{20}D$	Ir, cm^{-1} C=O	C=C	=CH	C—S
4a	89	63–65 (6)	1.5104	1790	1635	930	700
4b	82	88–95 (13)	1.5108	1790	1660	970	700
4c	70	82–87 (15)	1.5060	1790	1645	903	700
4d	71	94–97 (10)	1.4889	1795	1665	840	700

[a] Satisfactory analytical values (±0.3% for C and H) were reported for all compounds: Ed.

4-Methyl-3,6-dihydro-2*H*-thiopyran-3-one (6b).—Essentially the same procedure as described above for the cyclization of **4a** was employed. From 4.2 g of **4b** was obtained 1.0 g (30%) of **6b**: bp 99–103° (15 mm); $n^{20}D$ 1.5491; ir 1670 (C=O), 1080, 893 cm^{-1}; uv λ_{max} (95% EtOH) 245 mμ (ε 4810); nmr δ 1.78 (d, 3 H, J = 1.5 Hz), 3.18 (s, 2 H), 3.29 (m, 2 H), 6.70 ppm (m, 1 H). The semicarbazone had mp 187–190° dec (aqueous acetic acid).

Anal. Calcd for $C_7H_{11}ON_3S$ (semicarbazone): C, 45.39; H, 6.00; N, 22.69. Found: C, 45.43; H, 6.11; N, 22.79.

5-Methyl-3,6-dihydro-2*H*-thiopyran-3-one (6c).—The cyclization of **4c** was effected as described above: yield 49%; bp 85–95° (15 mm); $n^{20}D$ 1.5423 [lit.[2] bp 105–106° (6 mm); $n^{20}D$ 1.5579]; ir 1670 (C=O), 1273, 1023, 887 cm^{-1}; uv λ_{max} (95% EtOH) 242 mμ (ε 7850); nmr δ 2.00 (s, 3 H), 3.10 (s, 2 H), 3.15 (nearly s with fine splitting, 2 H), 5.78 ppm (double d, 1 H, J = 1.5 and 3.0 Hz). The semicarbazone had mp 149–152° dec (aqueous acetic acid).

Anal. Calcd for $C_7H_{11}ON_3S$ (semicarbazone): C, 45.39; H, 6.00; N, 22.69. Found: C, 45.21; H, 6.11; N, 22.53.

4-Isopropylidenetetrahydrothiophen-3-one (7d).—The acid chloride **4d** was similarly treated with aluminum chloride in TCE for 1.5 hr. The usual work-up afforded a ketonic product **7d**: yield 21%; bp 100–108° (13 mm); $n^{20}D$ 1.5520; ir 1690 (C=O), 1618, (C=C), 1270, 1200 cm^{-1}; uv λ_{max} (95% EtOH) 257 mμ (ε 8700); nmr δ 1.92 (s, 3 H), 2.21 (t, 3 H, J = 2 Hz), 3.26 (s, 2 H), 3.61 (t, 2 H, J = 2 Hz). The semicarbazone had mp 177–178° (AcOH).

Anal. Calcd for $C_8H_{13}ON_3S$ (semicarbazone): C, 48.22; H, 6.58. Found: C, 48.39; H, 6.68.

Registry No.—**3b**, 29431-24-1; **4a**, 29431-25-2; **4b**, 29520-65-8; **4c**, 29431-26-3; **4d**, 29431-27-4; **5a**, 29431-28-5; **5a** semicarbazone, 29431-29-6; **6a**, 29431-30-9; **6b**, 29431-31-0; **6b** semicarbazone, 29431-32-1; **6c**, 16994-29-9; **6c** semicarbazone, 29431-34-3; **7d**, 29520-66-9; **7d** semicarbazone, 29431-35-4; **8**, 19090-03-0; tetrahydrothiopyran-3-one 1,1-dioxide, 29431-37-6.

Acknowledgment.—The authors wish to express their gratitude to Mr. Mitsuo Sato for capable technical assistance in these experiments.

The Thermal Reorganization of Benzonorbornadiene

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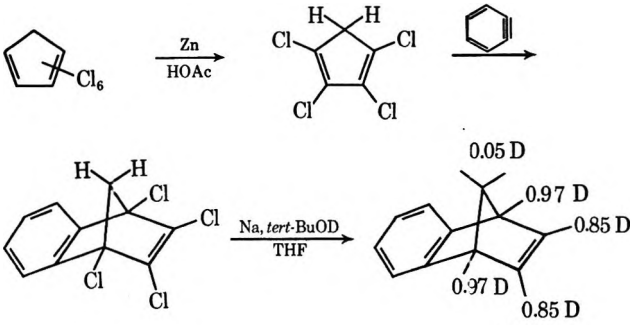
The thermal rearrangement of 2,3-benzonorbornadiene to 1,2-benzotropilidene has been shown, by deuterium labeling, to involve either benzonorcaradiene or 6,7-benzobicyclo[3.2.0]hepta-2,6-diene, or both. The norcaradiene valence tautomer of 1,2-benzotropilidene is ruled out as the first-formed intermediate.

Our interest in the thermal rearrangement of benzonorbornadiene (**1**) to 1,2-benzotropilidene (**2**) has led to a more detailed study of the mechanism of this reaction than previously reported.[3] We now wish to report on the thermal reorganization of the deuterium-labeled benzonorbornadiene (**3**) and its bearing on the mechanism of the reaction.

Treatment of hexachlorocyclopentadiene with zinc and glacial acetic acid afforded 1,2,3,4-tetrachlorocyclopentadiene[4] which, upon reaction with benzyne,[5] produced 1,4,5,6-tetrachloro-2,3-benzonorbornadiene, mp 92°, in 15% yield. The nmr spectrum (CCl_4) displayed an aromatic multiplet at τ 2.8 ppm and a singlet at τ 6.8 ppm, and the high-resolution mass spectral molecular weight confirmed the empirical formula. Treatment of the tetrachlorobenzonorbornadiene with sodium and *tert*-BuOD in THF, by a modification of the Winstein procedure,[6] afforded **3** in 82% yield. As needed, **3** was purified by preparative glpc. The deuterium content and distribution in **3** were determined by a com-



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(2) National Science Foundation Undergraduate Research Participant, Summer, 1968, at Case Western Reserve University.

(3) M. Pomerantz and G. W. Gruber, *J. Org. Chem.*, **33**, 4501 (1968).

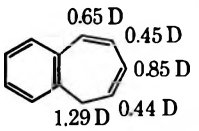
(4) E. R. Degginger and E. E. Gilbert, U. S. Patent 2,899,355; *Chem. Abstr.*, **53**, 22715*a* (1959).

(5) We are grateful to Professor Lester Friedman for the procedure for preparing the benzyne precursor, *o*-benzendiazoniumcarboxylate hydrochloride; *cf.* R. M. Roberts, J. C. Gilbert, L. B. Rodewald, and A. S. Wingrove, "An Introduction to Modern Experimental Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1969, p 198.

(6) (a) P. G. Gassman and P. G. Pape, *J. Org. Chem.*, **29**, 160 (1964); (b) P. Bruck D. Thompson, and S. Winstein, *Chem. Ind. (London)*, 405 (1960). We wish to thank the late Professor Winstein for a copy of the procedure.

bination of low voltage mass spectroscopy (3.68 deutrons/molecule) and nmr spectroscopy.[7]

When **3** was heated at 345° for 15 min (gas phase, Pyrex ampoule), it was observed to have undergone *ca.* 15% conversion to the benzotropilidene **4**. This low conversion was necessary to ensure minimal scrambling of the 3, 4, 6, and 7 hydrogens in the 1,2-benzotropilidene, although, of course, 1,5-hydrogen shifts equilibrate the hydrogens α to the benzene ring along with those β to the benezene ring.[3] Analysis of the deuterium content of **4** was by nmr spectroscopy.[8]



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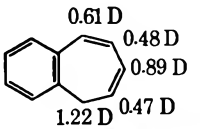
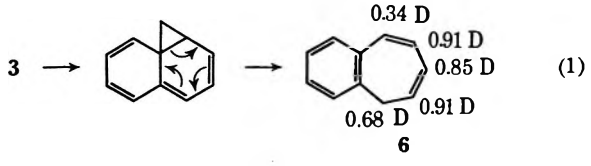


5

In a second run (340°, 66 min) the rearrangement proceeded to *ca.* 48% conversion and the deuterium labeling in the product was as indicated in **5**. Under these conditions the scrambling of positions 3 and 7 with 4 and 6 has already begun but has obviously not gone to equilibrium.[3]

If one considers the possible mechanisms which have not previously been eliminated,[3] we can now discount the following one (eq 1) since this would require the



(1)

6

labeling indicated in **6**. This leaves two possibilities as originally postulated by Cristol and Caple,[9] involving intermediates **7** or **8** (eq 2). In addition, if **8** was an intermediate it could give **7** (or its tropilidene valence tautomer). In either case, **7**, **8**, or valence tautomers could shift a hydrogen 1,5 (or 1,2; the overall result would be the same[3]) to produce **9** and finally **10** quite rapidly.[3] Conversion to **11** would occur subsequently if the reaction is allowed to go to more than 10 or 20% completion.[3] It is therefore seen that the observed deuterium distribution in **4** is, within experimental error, the same as predicted in eq 2.[10] In addition, **5** is seen to be intermediate in deuterium distribution between **10** and **11**.

It should be pointed out that in one reaction run to *ca.* 50% completion both recovered starting material and the product displayed, within experimental error, the same deuterium distribution (d_0, d_1, d_2, etc.) as the starting material as determined by mass spectroscopy.[11] Thus, no significant intermolecular scrambling occurs during the reaction.

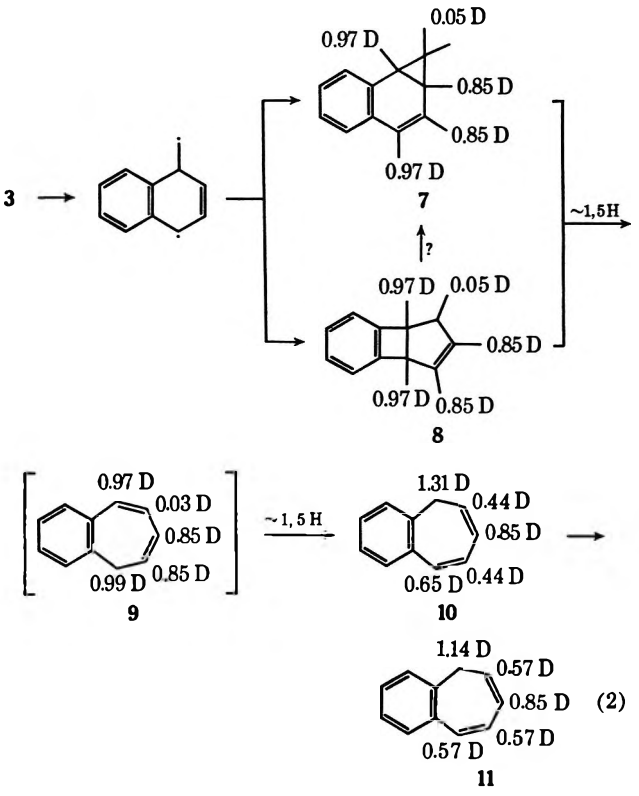
(7) The observation that there may be a trace of deuterium in the 7 position of **3** could be due to a trace of hexachlorocyclopentadiene in the tetrachlorocyclopentadiene which escaped glpc detection. The amount of deuterium is quite small, however, and might even be within experimental error of zero.

(8) In the case of **4** since we could not resolve the H_3 proton resonance from that of the aromatic protons, we assumed that H_3 contained half the amount of deuterium that was found in position 7.[3]

(9) S. J. Cristol and R. Caple, *J. Org. Chem.*, **31**, 585 (1966).

(10) If **10** had scrambled deuterium to the extent of *ca.* 10% (*i.e.*, 10% of **11**), this, too, would have been within the limits of experimental error.

(11) Unfortunately, for these determinations the voltage was slightly above the value which gives no fragmentation. Consequently a small P − 1 peak is present and thus the experimental error is larger than with the other mass spectra.



(2)

These experiments demonstrate the mechanism as shown in eq 2 involving either **7** or **8**, or both, as intermediates. In a large-scale pyrolysis using a flow system at 525° it was observed that the pot residue,[12] after distillation of the benzotropilidene through a Teflon spinning-band column, contained a trace amount of benzonorcaradiene. The material having the glpc retention time of benzonorcaradiene was collected. The nmr spectrum showed it to be mainly α- and β-methylnaphthalene and 1,2-benzotropilidene, but the peaks in the spectrum above τ 7.7 ppm were superimposable with those of authentic benzonorcaradiene.[13]

Thus, while the observation of benzonorcaradiene in the pyrolysis of benzonorbornadiene is consistent with the former being an intermediate on the way to 1,2-benzotropilidene, it does not itself prove the point. The present observations merely prove that one or both of the pathways depicted in eq 2 is the mechanism for the conversion of **1** to **2**.

Experimental Section

Mass spectra[14] were obtained on a Varian M-66, a CEC 21-492, or an AEI MS 902 mass spectrometer and nmr spectra on a Varian A-60A spectrometer equipped with a C-1024 time averaging computer. Infrared spectra were from a Perkin-Elmer 257 or a Beckman IR-8 spectrometer. Gas chromotography columns were (1) 5 ft by 0.25 in. 20% SE-30 silicone rubber on 60–80 mesh Chromosorb W, (2) 12 ft by 0.25 in. 20% Carbowax 20M on 60–80 mesh Chromosorb P, and (3) 5 ft by 0.125 in. 5% SE-30 silicone rubber on 60–80 mesh Chromosorb W. The 0.25-in. columns were used with a thermal conductivity detector instrument while column 3 was used with a flame ionization detector instrument. Melting points are uncorrected.

1,2,3,4-Tetrachlorocyclopentadiene.—The procedure was basically that of Degginger and Gilbert,[4] but with smaller quanti-

(12) We wish to thank Professor Lester Friedman and Mr. James C. Day, who ran this experiment, for a sample of their pot residue.

(13) We thank Dr. Gerald Gruber for this determination.

(14) We wish to thank Professor I. J. Borowitz of Yeshiva University, Mr. Harold Marsh of Case Western Reserve University, and Dr. Fred Abramson of CEC/Analytical Instruments Division for obtaining the mass spectra.

ties and longer time for the addition of zinc. In the first preparation, hexachlorocyclopentadiene (273 g, 1 mol) was mixed with 450 ml of glacial acetic acid in a 1-l. three-necked flask equipped with a thermometer, condenser, and stirrer. Zinc dust (150 g, 2.3 g-atoms) was gradually added to the rapidly stirred solution; the temperature of the very exothermic reaction was maintained below 75° with a Dry Ice–acetone bath. The addition required 55 min, after which the mixture was stirred for 35 min. The slurry which resulted was mixed with 1.5 l. of water. When the organic layer solidfied it was filtered from the aqueous layer and dissolved in ligroin. This was filtered free of zinc particles, dried, and reduced in volume with a rotary evaporator to obtain light yellow crystals, mp 59–60° (lit.[4] 61.6–62.4°), upon cooling. Glpc on column 3 at 100° showed the presence of a small amount of starting material.

In the second preparation, 136.5 g (0.5 mol) of hexachlorocyclopentadiene, 225 ml of glacial acetic acid, and 80 g (1.2 mol) of zinc dust were used. The addition time was 30 min, after which the mixture was stirred for 0.5 hr and treated the same as above.

The crystalline material, combined from both reactions, was sublimed under aspirator pressure to give a white solid (mp 61°) which showed no hexachlorocyclopentadiene by glpc (column 3 at 100°). The overall yield was 61.6 g (20% of theoretical); nmr (CCl_4) showed a singlet at τ 6.6 ppm.

o-**Benzenediazoniumcarboxylate Hydrochloride.**—The procedure of Friedman[5] was used in the preparation of this material. Into an 800-ml beaker surrounded by an ice bath was placed 27.4 g (0.2 mol) of anthranilic acid and 250 ml of absolute ethanol. The solution was stirred magnetically and when the temperature fell to 15° concentrated hydrochloric acid (23 ml) was added. Then isoamyl nitrite (55 ml) was slowly poured into the solution. This was stirred for 15 min, during which time light-colored granules began to appear. Absolute ether (250 ml) was added and the cold mixture was stirred for 30 min. The crystals were collected by suction filtration and washed with fresh absolute ether. The light pink solid was refrigerated until needed.

1,4,5,6-Tetrachloro-2,3-benzonorbornadiene.—The method of Friedman[5] was used. In a typical reaction 9.3 g (0.05 mol) of *o*-benzenediazoniumcarboxylate hydrochloride and 11.3 g (0.055 mol) of tetrachlorocyclopentadiene were dissolved in 100 ml of ethylene dichloride contained in a 500-ml three-necked round-bottomed flask equipped with a thermometer, condenser connected to a bubble counter, mechanical stirrer, and heating mantle. Propylene oxide (4.4 g, 0.075 mol) was added and the medium was vigorously stirred while being slowly heated to reflux temperature. Gas evolution occurred and frothing was kept to a minimum by rapid stirring. After gas evolution ceased, most of the solvent was distilled and the resulting red-orange slurry was treated with petroleum ether (bp 30–60°). The dark solution was filtered from the insoluble red-orange solid and the solvent was removed with a rotary evaporator. The resulting dark residue was steam distilled to obtain a light yellow solid which when recrystallized several times from hexane, gave a white solid, mp 92°. The nmr spectrum displayed a multiplet centered at τ 2.8 ppm and a singlet at τ 6.8 ppm in the ratio of 2:1 (yield 4.6 g, *ca.* 15% of theoretical). Mass spectrum.[14] Calcd for $C_{11}H_6{}^{35}Cl_4$: 277.9224. Obsd: 277.9222.

1,4,5,6-Tetradeuterio-2,3-benzonorbornadiene (3).—The Gassman[6a] modification of the Winstein[6b] procedure was employed in this reduction. A solution of 2.8 g (0.01 mol) of tetrachlorobenzonorbornadiene and 8.4 g (0.11 mol) of *tert*-butyl alcohol-*O*-*d* in 48 ml of dry tetrahydrofuran was prepared in a 100-ml, three-necked round-bottomed flask equipped with a nitrogen inlet, condenser connected to a bubble counter, thermometer, magnetic stirrer, and heating mantle. A dry nitrogen atmosphere was maintained, and sodium metal (6.0 g, 0.26 g-atom) was added in small quantities. The mixture was stirred and gradually heated to reflux. After 5 hr of refluxing, the mixture was stirred at room temperature for 2 days. The excess chunks of sodium were removed and methanol was added dropwise to the mixture. The resulting slurry was slowly poured onto 500 g of ice. The organic material was extracted with four 150-ml portions of ether, and the combined extracts were washed with three 200-ml portions of water and 200 ml of saturated sodium chloride solution. The ethereal solution was dried (anhydrous magnesium sulfate) and stripped of solvent; the brown-yellow oil was distilled under aspirator pressure to give a colorless liquid [bp 80–85° (55 mm), 1.1 ml, 1.3 g, 82% of theory]. Pure 1,4,5,6-tetradeuteriobenzonorbornadiene (**3**) was collected from glpc columns 1 or 2 operated at 195°. Low-voltage mass spectral analysis[14] indicated 3.68 deuterons per molecule, and nmr analysis gave the distribution indicated (**3**).

Pyrolysis of 1,4,5,6-Tetradeuterio-2,3-benzonorbornadiene (3).—Compound **3** (150 μl) was sealed under reduced pressure in a 50-ml base-washed Pyrex ampoule and heated for 1.1 hr at 340–343° (warm-up of 10 min from 308–340°). The product **5** and starting material were purified and analyzed by glpc (column 1 at 195°), which indicated about 47% reaction. Nmr analysis gave the deuterium distribution indicated in **5**.

A second pyrolysis of **3** (150 μl) at 342–345° for 15 min (warm-up of 10 min from 312–342°) followed by glpc analysis (column 2 at 195°) and purification indicated 15% conversion. The nmr spectrum of the product **4**, in CCl_4, was obtained with the aid of a Varian C-1024 time averaging computer.[15]

Registry No.—Benzonorbornadiene, 4453-90-1.

(15) We wish to thank the National Science Foundation for a grant toward the purchase of the time-averaging computer.

Addition of Trimethyltin Hydride and Methylhalotin Hydrides to Norbornadiene

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The additions of trimethyl-, dimethylchloro-, dimethylbromo-, dimethyliodo-, and methyldichlorotin hydrides to norbornadiene have been examined. Four isomeric products are formed in each case: norbornenes with the organotin function in the endo-5, exo-5, or syn-7 position, and nortricyclene with this function in the 3 position. The anti-7 isomer is not found and its absence is attributed to steric and torsional effects in the radical from which it would be formed. The endo-5 and syn-7 isomers, products of initial endo attack by the organotin radical, amount to nearly half of the total product. This high value appears not to be attributable in significant degree to coordination between tin atoms and double bonds either during the course of the reaction or in the products.

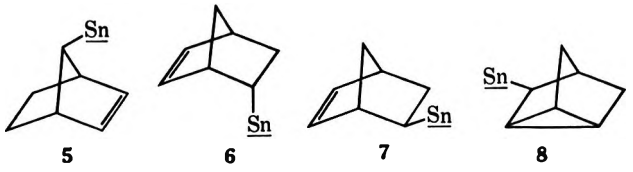
Free-radical additions to norbornadiene are of considerable interest because their study can reveal information about the existence of nonclassical homoallylic free radicals, about rearrangements, and about factors concerning position and stereochemistry of attack on double bonds by free radicals.[1] The existence of the homoallylic nonclassical free radical 1 (Scheme I) has been rendered highly improbable by work of Cristol, Brindell, and Reeder[2] on the effect of dilution on the distribution of products obtained in the addition of thiophenols to norbornadiene. More recent results are consistent with this conclusion. All of the products obtained in free-radical additions to norbornadiene can be understood in terms of the series of reactions and intermediates shown in Scheme I. Each of the six radicals can be converted into two epimeric products by atom abstraction from an appropriate donor. Thus, depending on the adding reagent, there could be formed up to four geometrical isomers of each of three structurally isomeric products, and each of the twelve could exist as a *dl* pair. Studies on substituted norbornadienes have been made by Davies[3a] and by Prilezhaeva[3b] and their coworkers. Which of the structural isomers are formed depends upon the substrate and addend. The stereochemistry depends upon the configuration and nature of substituents in the 7 position and upon the nature of the attacking free radical: electronic factors seem to dominate over steric factors.

Free-radical reaction of thiols with norbornadiene itself results in formation of the 1,2 adduct and the nortricyclyl isomer. Contrary to earlier reports, Van Auken and Rick[4] have shown that both *exo*- and *endo*-5-thiolacetoxybicyclo[2.2.1]hept-2-ene (in the ratio 2:1) are formed upon addition of thiolacetic acid; the only other low-molecular-weight product reported was 3-thiolacetoxynortricyclene.

As an extension of our earlier work on the norbornenyl–nortricyclyl free-radical system[5] and on the addition of trimethyltin hydride to dienes,[6] we have examined the addition of this hydride and of methylhalotin hydrides to norbornadiene, with particular reference to the structure and stereochemistry of the products formed. The free-radical chain mechanism for the addition of organotin hydrides to olefins not substituted by strongly electron-attracting groups has been deduced[7a,b] from evidence provided particularly by Neumann and coworkers,[7a,c] and the initial attack by the organotin radical has been shown to be reversible.[7c,8] Thus, kinetic control cannot be assumed to determine product distributions.

Results and Discussion

The reaction of trimethyltin hydride and norbornadiene was carried out by heating the reactants at 60° for several hours or by irradiation through Pyrex. Yields of isolated product amounted to 89–95%. Gas–liquid partition chromatography (glpc) using a column of 1,2,3-tris-2-cyanoethoxypropane on Diatoport P showed three peaks due to norborn-2-en-7-*syn*-yltrimethyltin (**5**) (Sn = Me_3Sn), *endo*-norborn-2-en-5-yltrimethyltin (**6**), and a mixture of *exo*-norborn-2-en-5-yltrimethyltin (**7**) and 3-nortricyclyltrimethyltin (**8**), in order of increasing retention time. When glpc was carried out using a column of Apiezon L on Chromosorb W, the order of elution was **5**, then **6** plus **7**, and then **8**. Each of the products has been fully characterized by elemental analysis, spectral properties,



5 **6** **7** **8**

and chemical reactions.[9] Each method of reaction led to the same product mixture, 11% of **5**, 35% of **6**, 43% of **7**, and 11% of **8**, and this distribution was independent of the extent of reaction, indicating no isomerization of the products under the reaction conditions.

Products **5** and **6** must be the result of initial endo attack on the diene by the trimethyltin radical, and some or all of **8** could also be. This amounts to about 50% of the total. None of the epimer of **5**, norborn-2-en-7-*anti*-yltrimethyltin, was observed. This was established by independent synthesis of both isomers

(1) See D. I. Davies and S. J. Cristol in "Advances in Free Radical Chemistry," Vol. I, G. H. Williams, Ed., Logos Press, London, England, 1965, pp 155 ff.

(2) S. J. Cristol, C. D. Brindell, and J. A. Reeder, *J. Amer. Chem. Soc.*, **80**, 635 (1958).

(3) For recent leading references, see (a) D. I. Davies and M. J. Parrott, *J. Chem. Soc. C*, 659 (1970); (b) E. N. Prilezhaeva, V. A. Asovskaya, G. U. Stepanyanz, D. Mondeshka, and R. J. Shekhtman, *Tetrahedron Lett.*, 4909 (1969).

(4) T. V. Van Auken and R. A. Rick, *ibid.*, 2709 (1968).

(5) C. R. Warner, R. J. Strunk, and H. G. Kuivila, *J. Org. Chem.*, **31**, 3381 (1966).

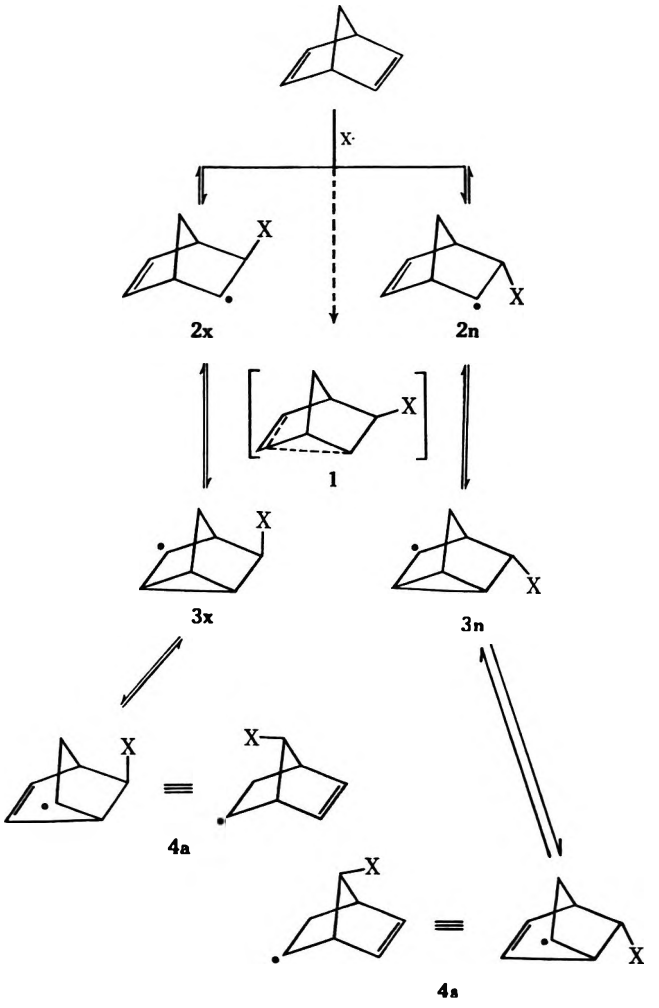
(6) R. H. Fish, H. G. Kuivila, and I. J. Tyminski, *J. Amer. Chem. Soc.*, **89**, 5861 (1967).

(7) (a) W. P. Neumann and R. Sommer, *Justus Liebigs Ann. Chem.*, **675**, 10 (1964); (b) H. G. Kuivila, *Advan. Organometal. Chem.*, **1**, 47 (1964); (c) W. P. Neumann, H. J. Albert, and W. Kaiser, *Tetrahedron Lett.*, 2041 (1967).

(8) H. G. Kuivila and R. Sommer, *J. Amer. Chem. Soc.*, **89**, 5616 (1961).

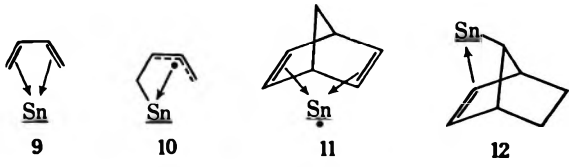
(9) H. G. Kuivila, J. D. Kennedy, F. L. Pelczar, and R. Y. Tien, unpublished results.

SCHEME I



and demonstration that they have different retention times on the Apiezon L column and that their proton magnetic resonance spectra show differences in both chemical shifts and coupling patterns.

The high incidence of products from endo attack was reminiscent of the high proportion of *cis*-crotyltrimethyltin formed in the addition of trimethyltin hydride to butadiene.[6] It was suggested that this might be due to formation of coordinated intermediates such as **9** or **10**. In the present case the diene could act as a bidentate ligand as in **11**. Similarly, the formation



of **5** to the exclusion of its epimer might gain impetus from coordination such as that shown in **12**. If this postulate is correct, increasing the Lewis acid character of the tin should result in diversion of more of the reaction toward formation of more **5** and **6** at the expense of **7**.

As one test of this postulate, we sought to determine whether proton magnetic resonance studies would provide any evidence for coordination of the type depicted in **11** with the organotin radical replaced by an organotin halide. This might alter the values of the chemical shifts of the protons of the methyl groups on the tin or the $^{119}Sn-^{1}H$ coupling constants, or both. The methyl proton chemical shifts of the three methyltin chlorides in 2–5% concentration were measured at 35° in carbon tetrachloride, benzene, and norbornadiene and are given in Table I. Included are four values

TABLE I

PROTON CHEMICAL SHIFTS OF METHYLTIN HALIDES[a]

Solvent	Me_3SnCl	Me_2SnCl_2	$MeSnCl_3$
CCl_4	9.34[b]	8.84[b]	8.39
C_6H_6	9.78[b]	9.66[b]	9.70
C_7H_8	9.51	9.07	8.71

[a] In τ units, at 35°; values to ±0.01 ppm. [b] At 23°, ref 10.

at 23° measured by Okawara and coworkers, but the temperature correction[10] would require our values to be increased by only about 0.03 ppm. The $^{119}Sn-^{1}H$ coupling constants are independent of temperature in this range. [Inclusion of data for tin(IV) chloride was not possible because of its exothermic reaction with norbornadiene.[11]] The data in Table I show that the proton resonance appears at a higher field in norbornadiene than in carbon tetrachloride and at a still higher field in benzene in which the shift is attributed to the magnetic anisotropy of the aromatic ring.[10] The data of Table II show that the $^{119}Sn-^{1}H$ coupling con-

TABLE II

$^{119}Sn-^{1}H$ COUPLING CONSTANTS OF METHYLTIN HALIDES[a]

Solvent	Me_3SnCl	Me_2SnCl_2	$MeSnCl_3$
CCl_4	58.2[a]	68.9[a]	96.9
C_6H_6	58.9[a]	69.3[a]	98.7
C_7H_8	57.5	69.1	98.8

[a] Values to ±0.6 Hz.

stants are substantially the same in the three solvents, whereas specific coordination would result in a considerable difference due to a change in orbital hybridization. The $^{119}Sn-^{1}H$ coupling constant of dimethyltin dichloride, for example, is 47-Hz greater in dimethyl sulfoxide than in carbon tetrachloride.[10] This is attributed to coordination between the sulfoxide oxygen with the tin atom. Because the coupling constant for a given organotin chloride is essentially the same in each of the three solvents, we may conclude that any coordination with norbornadiene is too weak to be manifested in the proton magnetic resonance spectra.

It was of interest to ascertain whether the type of coordination depicted in **12** could be detected in the norborn-2-en-7-*syn*-ylhalodimethyltins prepared by addition of the hydrides to norbornadiene. Such structures would seem to approach an optimum condition in which the interacting groups are held rigidly in close proximity to each other. When the organotin function is in the endo-5 position, the relationship is probably less ideal, and when it is in the exo-5 position interaction cannot occur. The nmr spectra of neat mixtures of the isomers formed in the addition reactions (see below) were examined and the results are shown in Tables III and IV.

(10) G. Matsubayashi, Y. Kawasaki, T. Tanaka, and R. Okawara, *Bull. Chem. Soc. Jap.*, **40**, 1566 (1967).

(11) F. M. Rabel and R. West, *J. Amer. Chem. Soc.*, **84**, 4169 (1962).

TABLE III
CHEMICAL SHIFTS OF TIN-METHYL PROTONS OF ADDUCTS TO NORBORNADIENE[a]

	Exo-5	Nortricyclyl	Endo-5	Syn-7
Me_3Sn	9.940	9.952	10.024	10.032
Me_2SnCl	9.925	9.442	9.530	9.53[b]
Me_2SnBr	9.323	9.339	9.430	9.43[b]
Me_2SnI	9.198	9.208	9.302	9.30[b]

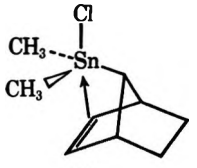
[a] In τ units at 37°; relative values accurate to ±0.003 ppm; absolute values to ±0.01 ppm. [b] Signals indistinguishable from those due to the *endo*-5 isomer.

TABLE IV
^{119}Sn-^1H COUPLING CONSTANTS OF NORBORNADIENE-ORGANOTIN HYDRIDE ADDUCTS[a]

	Exo-5	Nortricyclyl	Endo-5	Syn-7
Me_3Sn	49.5	50.65	50.2	51.1
Me_2SnCl	53.1	53.65	53.6	55.4
Me_2SnBr	52.3	52.8	52.8	54.55
Me_2SnI	51.15	51.75	52.0	53.5

[a] Values to ±0.2 Hz.

The differences among the chemical shifts of the Sn-methyl protons shown in Table III are small and probably reflect effects due to the position of these protons relative to the double bond. It is noted that the endo-5 and syn-7 methyl protons are slightly shielded in comparison with those of the nortricyclyl and exo-5 isomers. Somewhat larger variations result as the halogen is changed. In each isomer a downfield shift of the methyl protons occurs in the order Cl < Br < I. The ^{119}Sn-^1H coupling constants show small, but real, variations. In particular, the values for the syn-7 isomer are larger than those for either the endo-5 or the exo-5 isomer, and the difference is greater for the dimethylhalotin derivatives than for the trimethyltin derivative. If coordination occurs between the double bond and the tin atom as indicated in **12**, the configuration would tend toward that shown in **15**



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which approaches a trigonal bipyramidal configuration about the tin atom with the chlorine and double bond in the apical positions. In this structure the hybridization of the orbital on the tin atom through which it is attached to the methyl groups would tend from the original sp^3 toward sp^2. This increase in s character would lead to an increase in the coupling constant, as observed.[12] However, the changes in coupling constants are so small that it must be concluded that the interaction in question is very weak, at best.

Another test of the coordination postulate could be made by increasing the Lewis character of the tin atom used in the hydride addition. If it is valid, the result should be an increase in the proportions of adducts **5** and **6** at the expense of **7**. This was done by examining the addition of methylhalotin hydrides to norbornadiene.

(12) J. R. Holmes and H. D. Kaesz, *J. Amer. Chem. Soc.*, **83**, 3903 (1961).

Sawyer and Kuivila[13] showed that dialkylhalotin hydrides can be easily prepared by mixing dialkyltin dihydride and dialkyltin dihalide (eq 1), and Neumann

$$R_2SnH_2 + R_2SnX_2 \longrightarrow 2R_2SnHX \quad (1)$$

and Pedain[14] showed that they add readily to unsaturated hydrocarbons. Dimethylchlorotin hydride and norbornadiene reacted readily to provide a 94% yield of the isomeric adducts. The bromide and iodide were more reactive than the chlorohydride. The corresponding fluoro compound could not be prepared, presumably because of the extremely low solubility of dimethyltin difluoride. Methyldichlorotin hydride did not give good yields of adduct by the same procedure. This was undoubtedly due to complications in the addition reaction rather than in the exchange reaction of eq 2, for treatment of the reaction product

$$Bu_3SnH + MeSnCl_3 \rightleftharpoons Bu_3SnCl + MeSnCl_2H \quad (2)$$

mixture with methylmagnesium bromide gave about 90% of tributylmethyltin and only about 25% of the methylated hydride adducts.

Results obtained in the addition of these organohalotin hydrides and of trimethyltin hydride to norbornadiene are gathered in Table V. Clearly the product distribution is not affected profoundly by the replacement of methyl on the organotin hydride by halogen. However, the proportion of endo-5 isomer plus syn-7 isomer increases as methyls of trimethyltin hydride are replaced by one and two chlorines from 46 to 51 and 55%, respectively. As methyl is replaced by chlorine, bromine, and iodine, the proportion goes from 46 to 51 to 49 to 46%, respectively. Thus, there appears to be a small, but real, effect of increased electronegativity of the tin atom in increasing the proportion or products resulting from initial endo attack by the organotin radical. This is then counterbalanced by the steric effect as the size of the halogen atom is increased from chlorine to bromine to iodine.

The proportion of the syn-7 isomer shows no discernible trend as the nature of the hydride used is changed. As the dimethylhalotin hydrides produce less of this isomer than does trimethyltin hydride, involvement of the type of coordination depicted in **12** can be eliminated as the primary driving force for the formation of this isomer.

The absence of any anti-7 isomer in the product mixture is striking and requires explanation. Certainly initial exo attack by the trimethyltin radical, a primary requisite, is met as evidenced by the large amount of exo-5 adduct formed. Thus, radical **4a** is either not formed or does not go on to product by abstracting hydrogen from organotin hydride. The latter possibility appears to be the more likely one. There is good evidence that exo attack on radicals such as **4a** and **4s** is more facile than endo attack.[15] This is so because the hydrogen on the radical carbon (C-6) must pass through a conformation in which it is eclipsed with the hydrogen on the bridgehead carbon (C-1) if the attack is endo but not if the attack is exo (Scheme II). The nearer these hydrogens are to

(13) A. K. Sawyer and H. G. Kuivila, *Chem. Ind. (London)*, 260 (1961).
(14) W. P. Neumann and J. Pedain, *Tetrahedron Lett.*, 2461 (1964).
(15) For a recent review, see P. D. Bartlett, G. N. Fickes, F. C. Haupt, and R. Hegelson, *Accounts Chem. Res.*, **3**, 177 (1970).

TABLE V

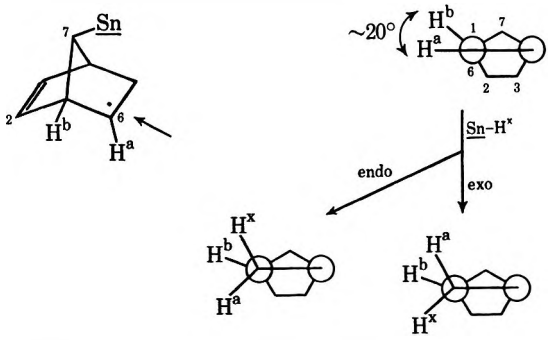
YIELDS AND PRODUCT DISTRIBUTIONS IN THE ADDITION OF THE METHYLTIN HYDRIDES TO NORBORNADIENE

Hydride	Yield, %	Product distribution, % Exo-5	Endo-5	Tricyclo	Syn-7
Me_2Sn	95	43 ± 1	35 ± 1	11 ± 1	11 ± 1
Me_2SnCl	94	41 ± 1.5	42.5 ± 1.5	8.0 ± 0.5	8.4 ± 0.5
Me_2SnBr	91	43 ± 1.5	38 ± 1.5	8.0 ± 0.5	10.8 ± 0.5
Me_2SnI	80[a]	46 ± 1.5	42 ± 1.5	8.2 ± 0.5	3.8 ± 0.5
	81[b]	48.5 ± 1.5	36.5 ± 1.5	7.5 ± 0.5	7.7 ± 0.5
$MeSnCl_2$	24[c]	32.5 ± 2.0	43.5 ± 2.0	12.7 ± 0.5	11.5 ± 1.0

[a] Norbornadiene added to iodohydride. [b] Reverse order of addition. [c] Yield of methylated product. Dichloride adduct not isolated.

SCHEME II

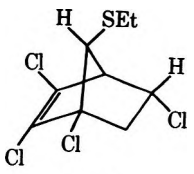
HYDROGEN TRANSFER TO C-6 OF NORBORNENYL RADICAL[a]



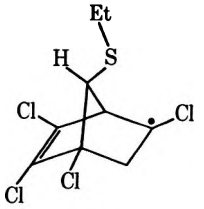
[a] In endo attack the dihedral angle of *ca.* 20° must pass through zero, whereas for exo attack it increases from 20°.

this eclipsed conformation in the transition state the greater is this torsional strain, which can amount to about 1 kcal.[16] A projection of a Dreiding model of **4a** is shown in Chart I. It is evident that the trimethyltin group forms a canopy over C-6 (as well as C-5) such that exo attack at C-6 is impossible. The model indicates that the closest point of approach of H_a and H_b to each other is less than 2 Å; the sum of the van der Waals radii is 2.4 Å! Furthermore, these nonbonded interactions are greater than those between the trimethyltin hydrogens and the nearest C-7 hydrogen in **2x**. Thus, the equilibrium **2x** ⇋ **3x** ⇋ **4a**, is shifted to the left. If the trimethyltin group is placed anti to C-6, forming **4s**, exo attack on the radical is not hindered. Also, nonbonded interactions involving the trimethyltin hydrogens are negligible in both **2n** and **4s** and should have little effect on the **2n** ⇋ **3n** ⇋ **4s** equilibrium. It may be concluded that the steric bulk of the trimethyltin group prevents the formation of the anti-7 isomer by virtue of the steric strain it introduces into the precursor radical and by steric blocking of hydrogen transfer from the exo side to C-6 of that radical.

Rearranged adducts of the anti-7 configuration have been obtained in other additions to norbornadienes. For example, 1,2,3,4-tetrachloronorbornadiene gives the exo and endo 1,2 adducts along with **13**, whose radical



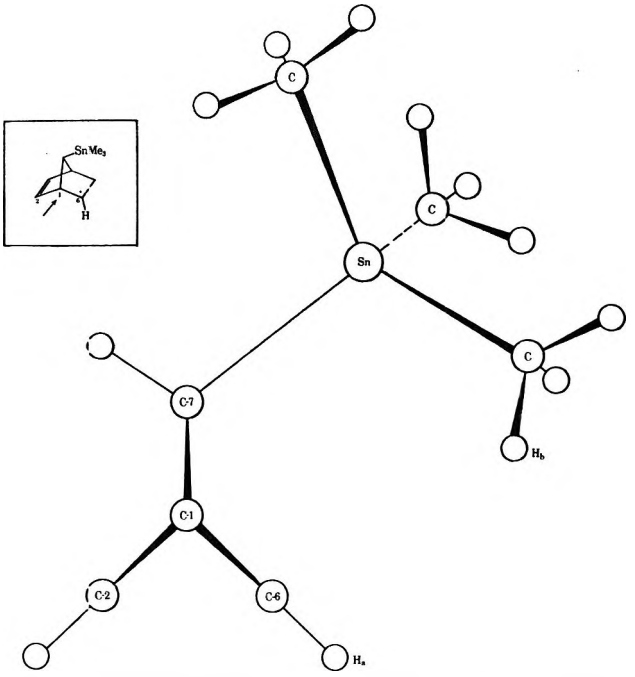
13



14

CHART I

END VIEW OF THE INTERMEDIATE NORBORN-2-EN-6-YL RADICAL[a]



[a] The radical shows the "canopy" effect of the trimethyltin group. Bond angles are not precise.

precursor must be **14**.[17] However, in this case the ethyl group can be rotated into conformations such as that shown, thus minimizing the steric obstruction to hydrogen atom transfer from the exo side.

Experimental Section

General.—Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer. Spectra were run on neat samples with tetramethylsilane as internal standard. Chemical shifts are recorded in τ values. Analyses were performed by Galbraith Laboratories. All operations involving organotin hydrides were conducted under nitrogen or argon.

Materials.—Dimethyltin dichloride, dimethyltin diiodide, dimethyltin difluoride, dimethyltin dibromide, and methyltin trichloride, bp 172–175°, mp 45°, were prepared and purified by standard procedures.

Trimethyltin hydride was prepared as previously described.[6] Tributyltin hydride was obtained by the reaction of tributyltin oxide with polymethylhydrosiloxane.[18] Dimethyltin dihydride, bp 36°, was made by an exchange reaction between tributyltin hydride and dimethyltin dichloride. Tri-*n*-butyltin hydride (33 g, 113 mmol) was added to 10 g (45 mmol) of dimethyltin dichloride in a flask equipped with a magnetic stirrer and a glass

(16) P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 699, 701 (1967).

(17) D. I. Davies and P. J. Rowley, *J. Chem. Soc. C*, 2249 (1967).

(18) K. Hayashi, J. Iyoda, and I. Shiihara, *J. Organometal. Chem.*, **10**, 81 (1967).

connection to a receiving vessel cooled to −70°. Pressure in the system was reduced slowly (compatible with the smooth evolution of the volatile dihydride) to 20 mm. The reaction vessel was then heated to *ca.* 60° for 15 min. The collected liquid was redistilled at atmospheric pressure, yielding dimethyltin dihydride, bp 36–37° (6.0 g, 88%). All processes were carried out under nitrogen. Norbornadiene was redistilled and stored in a refrigerator.

Addition of Trimethyltin Hydride to Norbornadiene. A.—To 46 g (0.5 mol) of freshly distilled bicycloheptaidene heated to 60° in an argon atmosphere was added 83 g (0.50 mol) of trimethyltin hydride over 1 hr. Heating was continued for an additional 3 hr. Distillation afforded a product (115 g, 95%), bp 40° (0.1 mm). Gas–liquid chromatography on a 15 ft × 0.25 in. column of 1,2,3-tris-2-cyanoethoxypropane on 60–80 mesh Diatoport showed three peaks with relative areas 11% (compound **5**), 36% (compound **6**), and 53% (compounds **7** and **8**). Glpc on an Apiezon L column changed the order of elution to **5**, then **6** plus **7**, and then **8**.

Anal. Calcd for $C_{10}H_{18}Sn$: C, 46.75; H, 7.01; Sn, 46.24. Found for mixture: 46.47; H, 6.95; Sn, 46.50. Found for **5**: C, 46.51; H, 6.94; Sn, 46.47. Found for **6**: C, 46.55; H, 6.96; Sn, 46.50; Found for **7** plus **8**: C, 46.58; H, 6.97; Sn, 46.43.

B.—A mixture of 5 g (52 mmol) of norbornadiene and 8.3 g (50 mmol) of trimethyltin hydride at 0° was irradiated in a Pyrex tube with a mercury vapor lamp for 6 hr. Distillation yielded 11.3 g (89%) of product with composition identical with that obtained in the thermal reaction as shown by glpc.[19]

Reaction of Dimethylchlorotin Hydride with Norbornadiene.—Dimethyltin dihydride (6.0 g, 40 mmol) was added to dimethyltin dichloride (8.3 g, 38 mmol) at −70°. A clear homogenous colorless liquid was produced on warming to room temperature and shaking. This was cooled to −70° and norbornadiene (9.0 ml, 108 mmol) was added; this was warmed to room temperature; shaking gave a clear colorless liquid. After 1 min, the evolution of heat was noted. The vessel was cooled from time to time in a bath at 0°. When the spontaneous reaction had ceased, the product was heated at 60° for 30 min and then distilled, yielding a mixture of dimethylnorbornenyltin chloride isomers, bp 68–70° (0.10 mm) (15.2 g, 94%), as a clear colorless liquid. *Anal.* Calcd for $C_9H_{15}ClSn$: C, 39.0; H, 5.4; Cl, 12.8. Found: C, 39.2; H, 5.4; Cl, 12.8.

Reaction of Dimethylbromotin Hydride with Norbornadiene.—Dimethyltin dihydride (4.2 g, 27.8 mmol) was added to dimethyltin dibromide (8.6 g, 27.8 mmol) at −70°. A homogenous clear colorless liquid was produced on warming to room temperature and shaking (mp >0°). This was cooled to −70°, and norbornadiene (6.0 ml, 72 mmol) was added. On warming, a vigorous exothermal reaction commenced before complete dissolution of the bromotin hydride had occurred; this was moderated by plunging the vessel into a bath at −70°. The mixture was again allowed to warm and was further moderated by cooling in a bath at 0°. When the spontaneous reaction had ceased, the product was heated at 65° for 40 min and then distilled, yielding a mixture of dimethylnorbornenyltin bromide isomers, bp 75–76° (0.30 mm) (16.3 g, 91%), as a clear colorless liquid.

Anal. Calcd for $C_9H_{15}BrSn$: C, 33.6; H, 4.66; Br, 24.8. Found: C, 33.7; H, 4.66; Br, 24.82.

Reaction of Dimethyliodotin Hydride with Norbornadiene. A.—Dimethyltin dihydride (4.3 g, 28.5 mmol) was added to dimethyltin diiodide (11.5 g, 28.6 mmol) at −70°. The mixture was warmed to room temperature and shaken, yielding a clear colorless liquid (mp 0°). To this was added slowly, with shaking and cooling in a bath at 0°, norbornadiene (7.0 ml, 68.5 mmol). The reaction was very exothermic, and slight effervescence occurred. The product was heated for 60 min at 65°, yielding a colorless liquid containing a small amount of white solid. Distillation under reduced pressure gave a forerun of dimethyltin diiodide and one main fraction, bp 78–80° (0.30 mm), a mixture of dimethylnorbornenyltin iodide isomers (16.9 g, 80%). A dark gray residue remained in the distillation flask.

B.—Dimethyltin dihydride (5.6 g, 37.1 mmol) and benzene (25 ml) were added to dimethyltin diiodide (14.9 g, 37.0 mmol) at −70°. The mixture was allowed to warm with shaking. As soon as a homogenous solution was formed (estimated temperature 6–10°), it was added to a cold solution of benzene (20 ml) and norbornadiene (8.0 ml, 79.0 mmol). No immediate reaction occurred. On warming of the mixture, the rate of temperature increase increased with temperature; this was maintained at 28–32° by cooling in a bath at 0°. When the spontaneous reaction had ceased (10 min), the solution was refluxed for 20 min leaving a clear colorless solution. Removal of the benzene and distillation as above gave a mixture of the dimethylnorbornenyltin iodide isomers, bp 76–78° (0.18 mm), together with a small amount of dimethyltin diiodide. The yield was 22.1 g (81%). An off-white residue remained in the flask.

Anal. Calcd for $C_9H_{15}ISn$: C, 29.4; H, 4.1; I, 34.4. Found for sample C: 29.1; H, 3.95; I, 34.2.

Attempted Reaction between Dimethyltin Difluoride, Dimethyltin Dihydride, and Norbornadiene.—Dimethyltin dihydride (5.3 g, 35.1 mmol) was added to dimethyltin difluoride (6.5 g, 34.9 mmol) and stirred, and norbornadiene (12 ml, 118 mmol) added. The suspension was stirred for 12 hr at room temperature and then for 12 hr at 60–70°; at this stage the infrared spectrum showed ν_{max} 1820 cm^{-1} (ν_{SnH}). The product was distilled at 100° (bath) yielding *no* dimethyltin dihydride, excess norbornadiene [bp 70–75° (ca. 400 mm)], and no further products, even after 1 hr at 0.10 mm. Tetrahydrofuran (20 ml) was added to the residual suspension, and a solution of methyl Grignard reagent, from methyl iodide (11.5 g, 81 mmol) and magnesium (1.8 g, 75 mg-atoms) in ether (35 ml), was slowly added dropwise with stirring. After refluxing for 6 hr the mixture hydrolyzed. Distillation gave no tetramethyltin and no products of the volatility expected for trimethylnorbornenyltin or dimethylnorbornenyltin or dimethylnorbornenyltin hydride. Only one product fraction, identified as a mixture of dimethylbis(norbornenyl)tin isomers, bp 87–89° (0.15 mm), was obtained (8.4 g, 72%).

Anal. Calcd for $C_{16}H_{24}Sn$: C, 57.4; H, 7.17. Found: C, 57.2; H, 7.24.

Reaction between Tributyltin Hydride, Methyltin Dichloride, and Norbornadiene.—A freshly prepared mixture of tributyltin hydride (10.90 g, 37.4 mmol) and norbornadiene (3.50 g, 38.1 mmol) was added, dropwise with stirring, to a solution of methyltin trichloride (9.0 g, 37.5 mmol) in ether (30 ml). A very exothermic reaction occurred. The vessel was cooled in a bath at 20° and the addition performed at such a rate as to maintain a gentle rate of reflux. After completion of the addition, the resulting white suspension was refluxed for 30 min. Ether (20 ml) was added and to the still refluxing suspension was added a solution of methyl Grignard reagent from methyl iodide (19 g, 134 mmol) and magnesium (3.0 g, 125 mg-atoms) in ether (35 ml) slowly with stirring. Refluxing was continued for 40 min. Work-up and distillation under reduced pressure gave a mixture of trimethylnorbornenyltin isomers, bp 42–46° (0.6 mm) (2.3 g, 24%), and tributylmethyltin, bp 73–74° (0.6 mm) (10.2 g, 89%). The product ratio of the trimethylnorbornenyltin mixture was determined as described below.

Determination of the Product Ratios Resulting from the Addition of Dimethylhalotin Hydrides and Methyldichlorotin Hydride to Norbornadiene.—Attempted glpc analysis of dimethylnorbornenyltin halide isomer mixtures on UCW 98, Apiezon L, and diethylene glycol succinate columns resulted in only qualitative separation. The proton magnetic resonance spectra, however, exhibited sufficient resolution for the Sn methyl protons so that, for all the dimethylnorbornenyltin halides, the ratio (exo-5 + tricyclo):(endo-5 + syn-7) could be determined with a maximum error estimated at ±1.5%. The smaller separation between the Sn methyl proton resonances of the trimethylnorbornenyltin isomers resulted in a slightly greater uncertainty (±2%) in the measurement of the same ratio for the methylated isomers of the methyltin dihalide hydride adducts. The amounts of tricyclo- and syn-7 isomers present in the dimethylnorbornenyltin halide mixtures were estimated by exhaustive methylation followed by glpc analysis of the resulting trimethylnorbornenyltin isomer mixture. A 6 ft × ⅛ in. 10% Apiezon L column gave sufficient resolution for the ratio of syn-7:(exo-5 + endo-5):tricyclo isomers to be determined with a maximum error estimated at ±0.5%; optimum results were obtained using Helium carrier gas, 30 lb/in.² inlet pressure, isothermal 140°, and a sample of 0.1 μl. From these pmr and glpc results the product ratios given in Table I were calculated.

That the results thus obtained reflect the isomer ratios of the original hydride addition is supported by the following. (a) Nmr monitoring of the reactions at all stages from just after the initial addition of the hydride to the distillation of the methylated

(19) Details on structural proofs, properties, and alternate syntheses will be submitted.

TABLE VI

SUMMARY OF REACTANT RATIOS AND YIELDS FOR THE METHYLATIONS OF DIMETHYLNORBORNENYLTIN HALIDES BY GRIGNARD REAGENT. THE PRODUCT IS TRIMETHYLNORBORNENYLTIN. WEIGHTS ARE IN GRAMS

X in $C_9H_{15}SnX$	Halide		Magnesium		Methy liodide		Product	
	Wt (g)	mmoles	Wt (g)	mg-atoms	Wt (g)	mmoles	Wt (g)	% yield
Cl	9.8	36	1.00	41.1	6.0	42.3	7.7	86[a]
Br	9.0	28	0.75	30.6	5.0	35.2	6.3	88
I	10.0	27	0.75	30.6	5.0	35.2	6.1	88 (A)
							6.3	91 (B)

[a] Some product lost due to sudden foaming during vacuum distillation; maximum pure yield must be a few per cent greater than this.

product showed that the ratio of (exo-5 + tricyclo):(endo-5 + syn-7) was constant. (b) The first and last cuts of a distillation of a dimethylnorbornenyltin halide mixture showed a similarly constant ratio. (c) An excess of Grignard reagent was used for each methylation, and completeness of methylation was verified by glpc analysis. Furthermore, all methylation yields were excellent. (d) The first and last cuts of a distillation of a trimethylnorbornenyltin mixture showed identical isomer ratios. (e) Treatment of a sample of a dimethylnorbornenyltin bromide isomer mixture with a deficiency of a methyl Grignard reagent showed no preferential reaction of the isomers under the conditions used for the complete methylation.

Methylation of Dimethylnorbornenyltin Halides.—The procedure for each of the halides was identical. That for the bromide is described here; the other reactions are summarized in Table VI. Methyl iodide (5.0 g, 35.2 mmol) in ether (20 ml) was added to magnesium (0.75 g, 30.6 mg-atoms); the mixture was refluxed briefly to allow complete dissolution of the metal. A sample of the dimethylnorbornenyltin bromide mixture (9.00 g, 28.0 mmol) in ether (20 ml) was added dropwise with stirring to the refluxing solution. A mildly exothermic reaction occurred. The solution was refluxed further for 40 min, cooled, and poured onto a mixture of sulfuric acid (1.5 ml) and crushed ice (50 g). The ethereal layer was separated, washed with 10% aqueous sulfuric acid (two 10-ml portions) and water (two 15-ml portions), dried over calcium chloride, and distilled, yielding ether and a methylation product, bp 42–48° (0.6 mm), as a clear colorless liquid (6.3 g, 88%).

Reaction of Dimethylnorbornenyltin Bromide with Deficiency of Methyl Grignard.—Magnesium (0.397 g, 16.5 mg-atoms) in ether (5 ml) was dissolved in methyl iodide (2.7 g, 19.0 mmol) in ethereal solution (15 ml), using the normal Grignard technique, and then added dropwise with stirring to a gently refluxing solution of dimethylnorbornenyltin bromide (10.1 g, 31.4 mmol). Refluxing was continued for 30 min; the mixture was cooled and shaken with 2% aqueous hydrobromic acid (100 ml). The aqueous layer was extracted with ether (two 25-ml portions). The combined ethereal extracts were washed with water (two 25-ml portions), dried over calcium chloride, and distilled, yielding ether, trimethylnorbornenyltin, bp 38–40° (0.5 mm) (3.2 g, 40%), and dimethylnorbornenyltin bromide, bp 77–79° (0.5 mm) (4.5 g, 44%). Nmr analysis of the original and final bromide mixtures and of the trimethyltin mixture showed that in each case the ratio (exo-5 + tricyclo):(endo-5 + syn-7) fell within the limits 51 ± 2.0:49 ± 2.0.

Registry No.—Trimethyltin hydride, 1631-73-8; norbornadiene, 121-46-0; dimethylchlorotin hydride, 16561-41-4; dimethylbromotin hydride, 16561-23-2; dimethyliodotin hydride, 16561-40-3.

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Halogenation with Copper(II) Halides. The Synthesis of Chloroiodoalkanes

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Vicinal chloroiodoalkanes have been synthesized by a simple, single-step reaction of olefins with copper(II) chloride and iodine or an iodine donor. The reaction is capable of application to substituted and unsubstituted olefins. Conjugated diolefins yield dichlorides *via* halide exchange reactions with initially formed chloroiodides.

The addition of halogens and of halogen derivatives to olefinic unsaturation has been the topic of substantial synthetic and mechanistic investigation.[1] While the interhalogen compounds, iodine and bromine monochloride, have been included in these studies as diagnostic tools for reaction mechanism, these reagents have been largely unexploited for synthetic purposes. The lack of simple and efficient syntheses for chloroiodoalkanes is particularly curious in view of the desirable agricultural[2] and chemical properties[3] exhibited by these organic halides.

Chloroiodoalkanes have not generally been prepared by the addition of preformed iodine monochloride to olefins. This is due to two factors: one is the necessity of preparing the reagent from the elemental halogens;[5] the other is the dissociable nature of the compound which frequently leads to high yields of unstable diiodides along with small amounts of desired product.[6–8] Attempts to generate chloroiodoalkanes through the addition of hydrogen iodide to olefinic chlorides have also been only partially successful owing

(1) H. P. Braendlin and E. T. McBee, "Friedel-Crafts and Related Reactions," Vol. III, G. A. Olah, Ed., Wiley, New York, N. Y., 1964, pp 1563–1579.

(2) (a) H. Johnston, U. S. Patent 2,808,444 (1957); (b) G. O. Turner, U. S. Patent 2,875,118 (1959).

(3) For example, the energy difference between the carbon–chlorine and the carbon–iodine bonds in 1-chloro-2-iodoethane permits its selective pyrolysis to vinyl chloride and iodine.[4]

(4) (a) E. T. Butler, E. Mandel, and M. Polanyi, *Trans. Faraday Soc.*, **41**, 298 (1945); (b) D. M. Fenton, U. S. Patent 3,205,517 (1965).

(5) L. F. Fieser and M. F. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 502.

(6) M. Simpson, *Justus Liebigs Ann. Chem.*, **125**, 101 (1863); **127**, 372 (1863).

(7) V. Voorhees and G. S. Skinner, *J. Amer. Chem. Soc.*, **47**, 1124 (1925).

(8) A. W. Francis, *ibid.*, **47**, 2340 (1925).

to the occurrence of rearrangement, halogen exchange, and reduction reactions.[9] Various β-chloroethyl phosphites have been treated with methyl iodide to give 70–85% yields of 1-chloro-2-iodoethane;[10,11] however, the reaction has limited synthetic scope since other requisite β-chloro alcohols are generally not available. A similar comment may be applied to the synthesis of chloroiodides by sodium iodide displacement on β-chloroalkyl sulfates.[12]

The *in situ* generation of iodine monochloride by the reaction of iodine with mercury(II), gold(I), silver(I), and copper(I) chlorides has been described.[13–15] When these reagents were combined in an ethereal solution of cyclohexene, 80–85% yields of 1-chloro-2-iodocyclohexane were recovered after 7–14 days at room temperature. Under these circumstances half of the halogen was degraded to inactive metal iodide. A related system was more recently described in which olefins were reacted with iodine and various Lewis acid metal chlorides in aqueous solution.[4b] Conversions based on iodine ranged from 30 to 60% indicating that much of the halogen was lost from the reaction, most likely through hydrolysis of alkyl iodide or conversion to metal iodide.

The reactions of olefins with copper(II) halides in various media have been a topic of investigation in these laboratories.[16,17] During these studies it was found that olefins reacted readily with copper(II) chloride and iodine to give high yields of vicinal chloroiodoalkanes. The remainder of this paper presents the scope and the utility of this novel synthetic procedure.

Results and Discussion

The general reaction of olefins with copper(II) chloride and iodine is illustrated by eq 1; typical yield data

$$2RCH{=}CHR + I_2 + 2CuCl_2 \longrightarrow 2RCH(Cl)CHR(I) + 2CuCl \quad (1)$$

are summarized in Table I. Gaseous olefins were reacted as solutions in various alkane, aromatic, or chlorocarbon solvents. Liquid olefins were allowed to react in the same diluents, or, alternatively, an excess of the olefinic substrate served as the reaction medium. Temperatures of 25–100° and reaction periods of a few minutes to 3–4 hr were required.

Although the reaction was generally insensitive to the choice of diluent, an exception was afforded by the reaction of ethylene in carbon tetrachloride. In this medium no chloroiodoethane was formed, and 1,2-diiodoethane was the sole product. Conversely, all olefins higher than ethylene reacted smoothly to give excellent yields of chloroiodides. While carbon tetrachloride would be anticipated to retard the reaction to some degree as a consequence of copper(II) complexation by the chlorocarbon,[18] this factor alone should not totally inhibit the ethylene reaction. The fact that the diiodides derived from other simple olefins are labile relative to diiodoethane under the reaction conditions,[19,20] indicates that facile dissociation of the diiodide contributes to driving the reaction to completion.

TABLE I
REACTION OF OLEFINS WITH COPPER(II) CHLORIDE AND IODINE

Olefin	Product	Yield, %
$CH_2{=}CH_2$	ICH_2CH_2Cl	82
$CH_3CH{=}CH_2$	CH_3CHCH_2I (73%), CH_3CHCH_2Cl (27%)	75
$CH_2{=}(CH_2)_3CH{=}CH_2$	$CH_3(CH_2)CHCH_2I$ (80%), $CH_3(CH_2)_3CHCH_2Cl$ (20%)	91
		95
$CH_2{=}CHOOCCH_3$	$ICH_2CHOOCCH_3$	88
$CH_2{=}CHCH{=}CH_2$	$ClCH_2CH{=}CHCH_2Cl$ (84%), $CH_2{=}CHCHCH_2Cl$ (16%)	78
$C_6H_5CH{=}CH_2$	$C_6H_5CHCH_2Cl$	79

Propylene and hexene-1 gave rise to mixtures of isomeric chloroiodoalkanes (Table I). The isomer distributions were comparable to those that had been observed in the addition of iodine monochloride to propylene.[21–23] Since the previous results had been interpreted in terms of an iodonium ion intermediate, which yielded ultimately Markovnikov (SN1) and anti-Markovnikov (SN2) products, it is apparent that a comparable specie is involved in the present case.

Vinyl acetate reacted smoothly with iodine and copper(II) chloride to give a single product, 1-chloro-2-iodoethylacetate (eq 2). The structure of this material was established in part by a positive iodoform test and reaction with 2,4-dinitrophenylhydrazine reagent.[24] In contrast to the difficulties experienced in adding iodine monochloride to vinyl acetate,[25] this facile addition was reminiscent of the rapid reaction observed during the addition of iodine isocyanate to

$$2CH_2{=}CHOOCCH_3 + I_2 + 2CuCl_2 \longrightarrow 2ICH_2CH(OOCCH_3)Cl + 2CuCl \quad (2)$$

(9) J. R. Shelton and L.-H. Lee, *J. Org. Chem.*, **23**, 1876 (1958).
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(17) W. C. Baird, Jr., and J. H. Surridge, *ibid.*, **35**, 3436 (1970).
(18) (a) D. C. Nonhebel, *J. Chem. Soc.*, 1216 (1963); (b) R. G. R. Bacon and H. A. O. Hill, *ibid.*, 1097 (1964).
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(25) D. Swern and E. F. Jordan, Jr., *J. Amer. Chem. Soc.*, **70**, 2334 (1948).

this olefinic ester.[26] The latter reaction has been shown to involve the electrophilic addition of iodonium ion,[27] and it is reasonable to consider a similar intermediate in this case.

The conjugated olefins, butadiene (eq 3) and styrene

$$2CH_2{=}CHCH{=}CH_2 + I_2 + 2CuCl_2 \longrightarrow 2\left\{\begin{matrix} ClCH_2CH{=}CHCH_2Cl \\ ClCH_2\underset{Cl}{\underset{|}{CH}}CH{=}CH_2 \end{matrix}\right\} + 2CuI \quad (3)$$

$$2C_6H_5CH{=}CH_2 + I_2 + 2CuCl_2 \longrightarrow 2C_6H_5\underset{Cl}{\underset{|}{CH}}CH\ Cl + 2CuI \quad (4)$$

(eq 4), did not yield chloroiodides but did produce high yields of the corresponding dichlorides. These results are attributed to the halide exchange reactions that occurred between initially formed chloroiodides and copper(I) chloride.[18b] The driving force for these exchange processes is provided by the reactivity of the carbon–iodine bonds in these dihalides and by the greater stability of copper(I) iodide relative to the chloride.[28] The dominance of the 1,4 isomer in the mixture of dichlorobutenes was a reflection of the equilibrium distribution over copper halides.[29]

While molecular iodine is a preferred iodine donor for the synthesis of chloroiodoalkanes, iodine may also be supplied to the reaction as a covalent metal iodide. The stoichiometry of this reaction is illustrated by eq 5; the Experimental Section gives representative results.

$$nRCH{=}CHR + 2nCuCl_2 + MI_n \longrightarrow n R\underset{Cl}{\underset{|}{CH}}\overset{I}{\overset{|}{CH}}R + 2nCuCl + MCl_n \quad (5)$$

These reactions proceeded with the release of elemental iodine in accord with the equilibrium shown in eq 6.[28b]

$$CuI + CuCl_2 \rightleftharpoons 2CuCl + {}^1/_2I_2 \quad (6)$$

While reactions involving metal iodides could be carried out in the hydrocarbon media previously cited, these systems were totally inhibited in carbon tetrachloride. This inhibition was attributed to the influence of chlorocarbon complexation on eq 6. Similarly, highly ionic iodides, *e.g.*, potassium iodide, were not suitable iodine donors, a fact which was also ascribed to the failure of the requisite redox reaction (eq 6) to occur.

The consideration of the mechanism operating in these reactions has precluded the intermediate participation of iodine monochloride (eq 7). If the inter-

$$I_2 + 2CuCl_2 \rightleftharpoons 2ICl + 2CuCl \quad (7)$$

halogen compound were being generated by this equilibrium, all olefins would be expected to yield chloroiodides independent of olefinic structure or reaction medium. The failure of ethylene to react in carbon tetrachloride has refuted this scheme. Less convincing, but supporting, evidence was the recovery of unchanged inorganic reagents in control reactions free of olefin.

A consistent picture of the reaction is provided by eq 8a–d. Two initial reactions are possible. One involves the addition of iodine to olefin catalyzed by copper(II) chloride[30] to generate the iodonium salt **3**. Alternatively, **3** arises from the interaction of iodonium complex **1** with copper(II) chloride. Loss of copper(II) chloride from **3** with concomitant addition of iodide yields the labile diiodide **2**. Transfer of chloride, however, irreversibly produces chloroiodoalkane **5** and the unstable copper(II) chloroiodide; the latter decomposes to copper(I) chloride and iodine (eq 8a). The appearance of copper(I) chloride in the system initiates the reaction sequence represented by eq 8c. The introduction of copper(I) iodide (eq 8c) in the presence of unreacted copper(II) chloride establishes reaction 8d. The net result of these individual steps is the general reaction previously illustrated by eq 1.[31]

While definitive analysis of such a complex system is difficult, the credibility of reactions 8b–d is provided by their independent observation.[13–15,19,28b] Reaction 8a is feasible by analogy to 8c. A consequence of this scheme is that limiting the initial charge of copper(II) chloride prevents the occurence of reaction 8d. In that case the reaction stoichiometry becomes that shown below. This reaction sequence also predicts

$$3RCH{=}CHR + 2CuCl_2 + 2I_2 \longrightarrow 3R\underset{I}{\underset{|}{CH}}\overset{Cl}{\overset{|}{CH}}R + CuCl + CuI$$

that swamping the system with olefin will depress the overall reaction rate owing to the increased concentration of olefin–iodine and olefin–copper(I) π complexes, which retard reactions 8a, 8c, and 8d. A reaction in neat cyclohexene (olefin:copper:iodine, 50:5:1 mol) required 4 hr to go to completion at room temperature; reaction of this olefin in *n*-pentane (olefin:copper: iodine, 2:2:1 mol) was >80% complete after 25 min.

The isomer distributions obtained with unsymmetrical olefins are ascribed to the reaction being governed by normal iodonium ion behavior in intermediates **3** and **4**. The facile reaction with vinyl acetate may be attributed to greater polarization of the reagents than was possible with iodine monochloride.[25] The formation of a single product from vinyl acetate is believed to reflect a unique bonding situation in the iodonium

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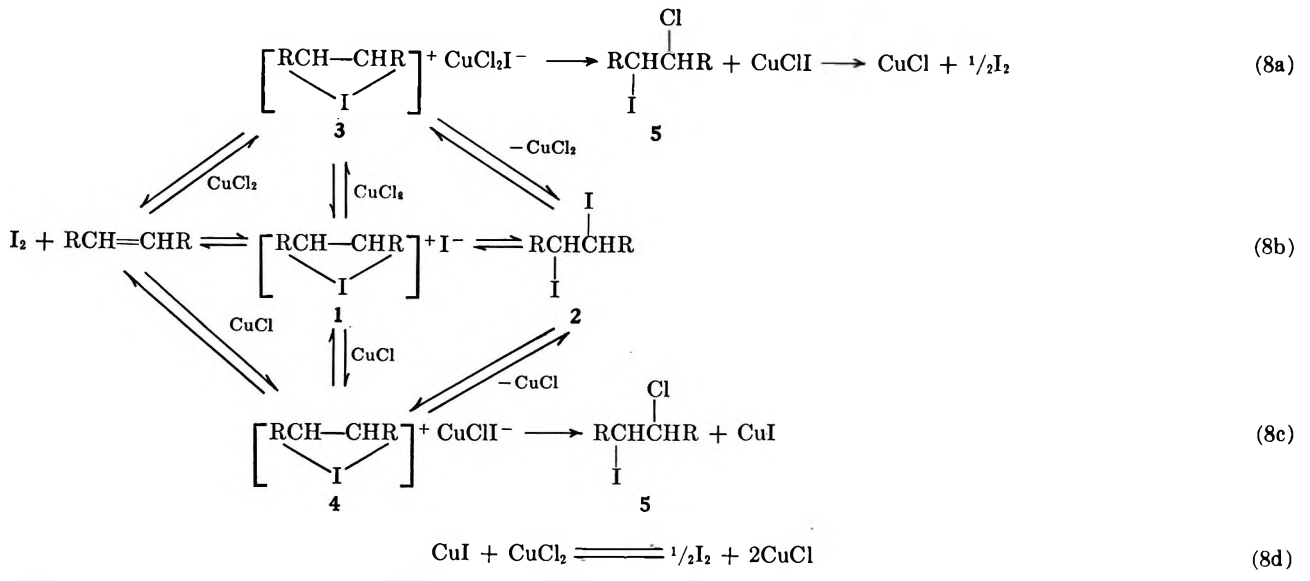
(28) (a) L. Pauling, "College Chemistry," W. H. Freeman and Co., San Francisco, Calif., 1951, pp 553–555; (b) "Gmelins Handbuch der Anorganischen Chemie," Vol. 60 (B1), Verlag Chemie, Weinheim, Ger., 1958, p 389.

(29) F. J. Bellringer and H. P. Crocker, British Patent 800,787 (1958).

(30) Copper(I) and copper(II) chlorides are known Lewis acids: G. A. Olah, "Friedel–Crafts and Related Reactions," Vol. I, G. A. Olah, Ed., Wiley, New York, N. Y., 1963, pp 215–216.

(31) A referee has suggested a free-radical mechanism for these reactions. A radical reaction had been considered and was rejected as being inconsistent with this and related studies. The $CuCl_2$–I_2 system has previously been shown to effect the iodination of aromatic rings *via* Lewis acid catalyzed iodonium ion attack,[17] a reaction analogous to eq 8a and 8c. A radical mechanism precludes the formation of copper(I) iodide, an observed reaction product, for a radical sequence yields ultimately only copper(I) chloride as the inorganic by-product. A radical reaction for eq 8c requires the formation of metallic copper, which has not been observed in copper(II) chloride deficient reactions where copper(0) would not be removed by disproportionation to copper(I) chloride ($Cu + CuCl_2 \rightarrow 2CuCl$).



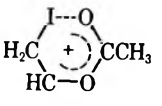
(8a)

(8b)

(8c)

(8d)

ion which tends to localize and stabilize the positive charge on the methine carbon (**6**).



6

Experimental Section

Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. Vapor phase chromatography (vpc) was performed utilizing a Perkin-Elmer 154D fractometer, a Perkin-Elmer Model 226 gas chromatograph, and a Varian Aerograph Model 202 gas chromatograph. Nmr spectra were recorded on a Varian Associates A-60 spectrometer using tetramethylsilane as an internal standard. Melting points and boiling points are not corrected. All reagents were obtained from commercial sources and were used as received. All gaseous olefins were CP grade.

Synthesis of Vicinal Chloroiodoalkanes. Ethylene.—Into a Parr high pressure reactor[32] were placed 200 ml of cyclohexane, 26.6 g (0.2 mol) of copper(II) chloride, 25.4 g (0.1 mol) of iodine, and 0.2 mol of ethylene. The reaction was stirred at 75–85° for 2 hr. The reaction mixture was filtered to give 23.5 g of copper salts, which corresponded to 12.3 g (0.125 mol) of copper(I) chloride, 4.7 g (0.025 mol) of copper(I) iodide, and 6.7 g (0.05 mol) of unreacted copper(II) chloride. From the filtrate was recovered 31.2 g (0.17 mol) of 1-chloro-2-iodoethane (85%): bp 55–57° (37 mm); n^{25}D 1.5636; d^{25} 2.12; nmr (neat) δ 3.2–3.6 (m, 2, HCCl), 3.7–4.1 (m, 2, HCI). Vpc analysis (2 m × 0.25 in. 20% diethylene glycol succinate column, 125°, 15-psig helium) gave a single peak, r_t 5.1 min from air. *Anal.* Calcd for C_2H_4ClI: C, 12.61; H, 2.12; Cl, 18.62; I, 66.65. Found: C, 12.91; H, 2.34; Cl, 18.80; I, 67.70.

If the reaction was performed at room temperature, no chloroiodoethane was produced. From the reaction was recovered unreacted copper(II) chloride and a 98% yield of 1,2-diiodoethane; the latter was shown to be identical with an authentic sample.

The reaction was repeated using a stoichiometric deficiency of copper(II) chloride; the reactor was charged with 0.3 mol of ethylene, 0.2 mol of copper(II) chloride, and 0.2 mol of iodine. From the reaction was isolated 54.5 g (96%) of 1-chloro-2-iodoethane and 29.3 g of copper(I) salts. The latter was a mixture of 0.1 mol of copper(I) chloride and 0.1 mol of copper(I) iodide.

When the reaction of ethylene was performed in carbon tetrachloride, an 80% yield of diiodoethane was isolated. A 10-g sample of this diiodide was refluxed with 5 g of copper(II) chloride in 50 ml of carbon tetrachloride for 2 hr. The bulk of the diiodide (91%) was recovered unchanged.

Propylene.—The same procedure was followed as described for ethylene. The yield of chloroiodopropanes was 75–80%; bp 54–55° (24 mm); n^{25}D 1.5403; nmr (neat) δ 1.65 (d, 2.3, CH_3-CHCl), 1.95 (d, 0.7, CH_3CHI), 3.2–4.4 (m, 3, CH_2, CH). Analysis of the methyl group areas showed the composition of the product to be 76.5% 1-iodo-2-chloropropane and 23.5% 1-chloro-2-iodopropane.

Cyclohexene.—Into a round-bottom flask were placed 50 ml of cyclohexene, 13.3 g (0.1 mol) of copper(II) chloride, and 12.7 g (0.05 mol) of iodine. The reaction was stirred at room temperature for 4 hr. The reaction mixture was filtered, and the filter cake was washed with *n*-pentane to give 9.8 g (0.1 mol) of copper(I) chloride. From the filtrate was isolated 24.2 g (99%) of 1-chloro-2-iodocyclohexane: bp 37° (0.2 mm); n^{25}D 1.5700; nmr (neat) δ 4.4 (m, 2, HCCl, HCI), 1.2–2.8 (m, 8, CH_2). Vpc analysis (2 m × 0.25 in. 20% diethylene glycol succinate column, 125°, 15 psig) gave a single compound, r_t 31.4 min. *Anal.* Calcd for $C_6H_{10}ClI$: C, 29.47; H, 4.12; Cl, 14.50; I, 51.90. Found: C, 29.57; H, 4.13; Cl, 14.40; I, 51.40.

A duplicate experiment was permitted to stir at room temperature for 15 min. Filtration gave 12.3 g of copper(II) chloride (93% recovery); from the filtrate was obtained ~20 g of a mixture of cyclohexene and iodine.

In another experiment a solution of 8.2 g (0.1 mol) of cyclohexene in 50 ml of pentane was stirred with 13.3 g (0.1 mol) of copper(II) chloride and 12.7 g (0.05 mol) of iodine at room temperature for 25 min. The reaction produced 20.0 g (82%) of chloroiodocyclohexane and 12.7 g of a mixture of copper(I) chloride (6.3 g, 0.064 mol), copper(I) iodide (3.4 g, 0.018 mol), and copper(II) chloride (2.4 g, 0.018 mol).

A mixture of 15 ml (0.15 mol) of cyclohexene, 13.3 g (0.1 mol) of copper(II) chloride, 25.4 g (0.1 mol) of iodine, and 50 ml of cyclohexane was stirred at room temperature for ~20 hr. A 95% yield of chloroiodocyclohexane was isolated. The inorganic product (14.4 g) was a mixture of 4.9 g (0.05 mol) of copper(I) chloride and 9.5 g (0.05 mol) of copper(I) iodide.

Hexene-1.—A mixture of 100 ml of hexene-1, 27 g (0.2 mol) of copper(II) chloride, and 26 g (0.1 mol) of iodine was stirred at reflux for 15 min. From the reaction was isolated 44.7 g (91%) of isomeric chloroiodohexanes. The nmr spectrum indicated a mixture containing 80% 1-iodo-2-chlorohexane and 20% 1-chloro-2-iodohexane.

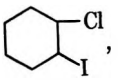
Vinyl Acetate.—To 100 ml of vinyl acetate was added 26 g (0.1 mol) of iodine and 27 g (0.2 mol) of copper(II) chloride. The reaction was stirred at 80° for 2 hr. The usual work-up gave 50.1 g (88%) of 1-chloro-2-iodoethylacetate: bp 38–40° (0.15 mm); nmr (neat) δ 6.50 (t, 1, HC<), 3.68 (d, 2, CH_2), 2.15 (s, 3, CH_3CO). *Anal.* Calcd for $C_4H_6ClIO_2$: C, 19.33; H, 2.44; Cl, 14.27; I, 51.07. Found: C, 20.07; H, 2.36; Cl, 14.40; I, 50.10. The ester gave a positive iodoform test; reaction with 2,4-dinitrophenylhydrazine reagent gave a dark red crystalline product, mp 80° dec. *Anal.* Calcd for $C_8H_6N_4O_4$: C, 43.25; H, 2.72; N, 25.26. Found: C, 43.31; H, 2.89; N, 24.56.

Iodine Donors and Diluents for Synthesis of Chloroiodoalkanes.—Cyclohexene was used as a model olefin. In a typical experiment a solution of 16.4 g (0.2 mol) of cyclohexene in 100 ml of inert diluent was heated and stirred with 26.6 g (0.2 mol) of

(32) 4500 Series, Parr Instrument Co., Moline, Ill.

copper(II) chloride and the indicated quantity of iodine donor. The reaction mixture was worked up in the usual manner. The results are summarized in Table II.

TABLE II



Diluent	Iodine donor[a]	Temp, °C	Time, hr	yield, %
C_6H_{12}	I_2	60	0.3	88
C_6H_6	I_2	80	0.1	91
CCl_4	I_2	80	0.1	90
C_6H_{10}[b]	CuI	80	1	83
C_6H_{10}	KI	80	2	0
C_6H_{10}	LiI	80	4	92
C_6H_{10}	BiI_3[c]	80	2	93
CCl_4	CuI	80	2	0
C_7H_{16}	CuI	98	2	66

[a] 0.1 mol. [b] 100 ml of cyclohexene as diluent. [c] 0.02 mol.

Reaction of Conjugated Olefins. Butadiene.—A Parr reactor was charged with 100 ml of benzene, 26.6 g (0.2 mol) of copper(II) chloride, 25.4 g (0.1 mol) of iodine, and 0.2 mol of butadiene. The reaction was stirred at 70° for 2 hr. The reaction mixture was filtered to give 37 g of copper(I) iodide. The benzene was removed from the filtrate on a rotary evaporator, and the residue was distilled to give 19.4 g (78%) of isomeric dichlorobutenes, bp 48–53° (14 mm). Vpc analysis (5 ft × 0.25 in. 20% diethylene glycol succinate column, 125°, 48 ml/min) gave the following isomer distribution: 3,4-dichlorobutene-1, 16% (r_t 3.7 min); *cis*-1,4-dichlorobutene-2, 3% (r_t 10.0 min); *trans*-1,4-dichlorobutene-2, 81% (r_t 12.0 min). The products were identified by comparison with authentic samples.

If 0.1 mol of copper(I) iodide was used as the iodine source, a 23% yield of dichlorobutenes was realized after 3 hr at 70°. When carbon tetrachloride was used as a reaction diluent, no reaction occurred with copper(I) iodide. This diluent in combination with molecular iodine gave a 90% yield of dichlorobutenes in 90 min.

In a control experiment 1 g (4.6 mmol) of 1-chloro-4-iodobutene-2[2c] and 1 g (10.2 mmol) of copper(I) chloride were stirred at 70° for 90 min in 10 ml of benzene. The benzene solution was analyzed by vpc and was shown to contain the three isomeric dichlorobutenes; the isomer distribution was comparable with that described above.

Styrene.—To a mixture of 13 g (0.05 mol) of iodine, 13.3 g (0.1 mol) of copper(II) chloride, and 60 ml of *n*-octane at reflux was added dropwise a solution of 10.4 g (0.1 mol) of styrene in 40 ml of *n*-octane. The addition required ~40 min.; the reaction was maintained at reflux for an additional 10 min. The reaction mixture was cooled and filtered to give 17.6 g of copper(I) iodide (theory, 19.0 g). The filtrate was washed with 20% sodium thiosulfate solution and was dried over magnesium sulfate. The *n*-octane was removed on a rotary evaporator [60° (15 min)] to give 17.4 g of crude product. Distillation gave 13.8 g (79%) of 1,2-dichloro-1-phenylethane: bp 67–73° (0.2 mm); nmr (neat) δ 7.2 (s, 5, C_6H_5–), 4.85 (t, 1, >CHCl), 3.75 (d, 2, $-CH_2Cl$). Vpc analysis [2 m × 0.25 in. 20% silicone (DC-200) column, 150°, 105 ml/min] showed a single peak, r_t 16.0 min; a small amount of styrene, r_t 2.6 min, was present as an impurity (~3–5%). *Anal.* Calcd for $C_8H_8Cl_2$: C, 54.89; H, 4.60; Cl, 40.51. Found: C, 54.92; H, 4.47; Cl, 39.67.

A sample of the dichlorophenylethane was dehydrochlorinated with methanolic sodium hydroxide to give α-chlorostyrene: bp 74–77° (14 mm); $n^{25}D$ 1.5561 (lit.[21] $n^{25}D$ 1.5590); nmr (neat) δ 7.1–7.5 (m, 5, C_6H_5), 5.43 (q, 2, $=CH_2$).

The reaction of styrene was repeated at room temperature for a period of 20 hr. The reaction produced 4.5 g (26%) of dichlorophenylethane and 8.6 g (0.083 mol) of polystyrene. The inorganic by-product was a mixture of unreacted copper(II) chloride (6.0 g) and copper(I) iodide (11.8 g); unreacted iodine (0.02 mol) was determined by titration with thiosulfate.

Registry No.—Copper(II) chloride, 7447-39-4; 1-chloro-2-iodoethane, 624-70-4; 1-iodo-2-chloropropane, 29568-69-2; 1-chloro-2-iodopropane, 29568-70-5; 1-chloro-2-iodocyclohexane, 29641-86-9; 1-chloro-2-iodoethylacetate, 29568-71-6; 1,2-dichloro-1-phenylethane, 1074-11-9.

Paramagnetic Metallocenes. Oxidation of Ferrocenyl Ketones[1]

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Ferrocenyl ketones which have an α-methylene group were oxidized to the stable paramagnetic semidiones. An excess of oxygen resulted in ortho oxygenation of the metallocene ring. The esr spectra indicated a remarkably small amount of electron spin delocalization into the metallocene ring. The simplicity of the esr spectra permitted the elucidation of the relative rates of semidione formation as a function of substituent on metal ion. Interannular substituent effects on electron distribution were shown to be primarily inductive in nature. Hydrogen–deuterium exchange of alkyl hydrogens α to the semidione when the oxidation was conducted in DMSO-d_6 was very slow; this observation was interpreted in terms of a dianion in the exchange reaction.

Ketones with an α-methylene group can be oxidized with molecular oxygen to the corresponding semidiones in dimethyl sulfoxide (DMSO) solution containing an excess of potassium *tert*-butoxide. The reaction is quite general and many semidiones prepared by this technique have been observed by esr spectroscopy.[2] Since our initial report on the conveniently prepared and stable semidione derivatives of metallocenes,[3] other stable metallocene radicals have been observed by esr.[4–7] These species are of interest from a viewpoint of electron spin delocalization, metal ligand interaction, and chemical reactivity. Despite the application of metallocenes as antioxidants, combustion control additives, photoprotecting uv absorbers, and medicinals (areas which clearly involve radical chemistry), the chemical and physical properties of stable metallocene radicals have been almost uninvestigated[8] until very recently. Most of the previous studies concerning radi-

(1) Supported by the Petroleum Research Fund administered by the American Chemical Society (Grant 1375-G1).

(2) G. A. Russell, *et al.*, *Rec. Chem. Progr.*, **27**, 3 (1969); and E. I. Kaiser and L. Kevan, Ed., "Radical Ions," Wiley, New York, N. Y., 1969, Chapter 3.

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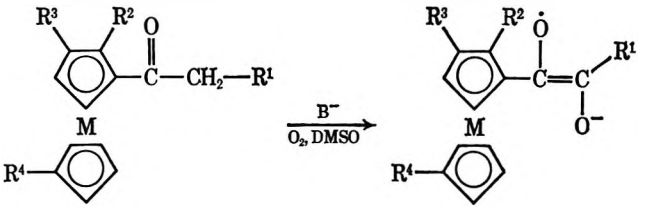
TABLE I

HYPERFINE SPLITTING CONSTANTS OF RADICALS OBSERVED ON INITIAL OXIDATION



X	M	R¹	R²	R³	R⁴	Xa	a^H, gauss	g
1	Ru	CH_3	H	H	H	1a	4.25 (3 H), 0.54 (2 H)	2.00642
2	Fe	CH_3	H	H	H	2a	4.20 (3 H), 0.50 (2 H)	2.00706
2′	Fe	CH_3	2,5-Dideuteriopropionylferrocene			2′a	4.20 (3 H), D not observed	2.00706
2″	Fe	CH_3	Propionylferrocene-d_9			2″a	4.20 (3 H), D not observed	2.00706
3	Fe	CH_2CH_3	H	H	H	3a	3.80 (2 H), 0.50 (2 H)	2.00703
4	Fe	$CH(CH_3)_2$	H	H	H	4a	1.75 (1 H), 0.50 (2 H)	2.00699
5	Fe	$CH_2CH(CH_3)_2$	H	H	H	5a	3.40 (2 H), 0.50 (2 H)	2.00696
6	Fe	C_6H_5	H	H	H	6a	1.70 (3 H), 0.50 (4 H)	2.00666
7a	Fe	CH_3	$COCH_3$	H	H	7a[a]	4.38 (3 H)	2.01604
							3.47 (4 H), 0.43 (2 H)	2.00790
8	Fe	CH_3	$CH_2CH_2CH_2CH_3$	H	$CH_2CH_2CH_2CH_3$	8a	4.35 (3 H), 0.42 (3 H)	2.00714
9	Fe	CH_3	CH_3	H	CH_3	9a	4.30 (3 H), 0.45 (4 H)	2.00717
10	Fe	CH_3	p-C_6H_4Cl	H	H	10a	4.17 (3 H), 0.50 (1 H)	2.00694
11	Fe	CH_3	H	$CH_2CH_2CH_2CH_3$	$CH_2CH_2CH_2CH_3$	11a	4.25 (3 H), 0.50 (2 H)	2.00737
12	Fe	CH_3	H	CH_3	CH_3	12a	4.25 (3 H), 0.50 (2 H)	2.00742
13	Fe	CH_3	H	p-C_6H_4Cl	H	13a	4.20 (3 H), 0.50 (2 H)	2.00680
14	Fe	CH_3	H	H	$C(CH_3)_3$	14a	4.20 (3 H), 0.50 (2 H)	2.00706
15	Fe	CH_3	H	H	p-C_6H_4Cl	15a	4.00 (3 H), 0.52 (2 H)	2.00749
16	Fe	CH_3	H	H	Br	16a	3.95 (3 H), 0.55 (2 H)	2.00700
17	Fe	CH_3	H	H	Adamantyl ketone	17a	3.85 (3 H), 0.52 (2 H)	2.00728
18	Fe	CH_3	H	H	$COC(CH_3)_3$	18a	3.83 (3 H), 0.52 (2 H)	2.00728
19	Fe	CH_3	H	H	$COCH_2CH(CH_3)_2$	19a	3.82 (3 H), 0.55 (2 H)	2.00728
							1.55 (1 H), 0.55 (2 H)	2.00729
20	Fe	CH_3	H	H	$COOCH_3$	20a	3.82 (3 H), 0.55 (2 H)	2.00728
21	Fe	CH_3	H	H	$COCH_2CH_2CH_3$	21a	3.80 (3 H), 0.55 (2 H)	2.00728
							3.55 (2 H), 0.55 (2 H)	2.00729
22	Fe	CH_3	H	H	$COCH_3$	22a	3.80 (3 H), 0.55 (2 H)	2.00728
23	Fe	CH_3	H	H	p-$COC_6H_4CH_3$	23a	3.72 (3 H), 0.55 (2 H)	2.00739
24	Fe	CH_3	H	H	CN	24a	3.72 (3 H), 0.55 (2 H)	2.00709

[a] 7 gives anomalous esr signals believed to arise from intramolecular condensation to form the p-benzoquinone type radical anions.

cal chemistry of metallocenes have been in the area of synthetic intermediates and one-electron oxidation of Fe^{2+} to Fe^{3+}.[9] In this paper some aspects of metallocene chemistry are discussed in terms of the stable paramagnetic semidione intermediate.

Results and Discussion

Ketones 1–24 (Table I) are oxidized initially to semidiones under conditions described in the Experimental Section. The experimental data shown in Table I provide an unambiguous assignment of the hyperfine splitting constants to the individual hydrogen atoms.

The quartet splitting of 4.20 G for entry 2 in Table I is assigned to the methyl hydrogens α to the semidione. As CH_3 is replaced by CH_2CH_3 and $CH(CH_3)_2$, the quartet splitting is respectively replaced by a triplet splitting from 2 H of 3.80 G and a doublet splitting from 1 H of 1.75 G.[10] When the ortho metallocene hydrogens are replaced with deuterium, the two 0.5-G hydrogen hyperfine splittings (Figure 1A) are replaced with deuterium hyperfine splittings of 0.50/6.5 G which are observed only as line broadening (Figure 1B). The replacement of an ortho hydrogen by CH_3 (entry 9 of Table I) results in the appearance of a hyperfine splitting pattern which requires the interaction of 4 H, $a^H = 0.45$ G, indicating that the CH_3 hyperfine splittings are the same as the hydrogen they replace. This is taken as evidence for a π delocalization mechanism into the metallocene ring in which a spin polarization mechanism places the same amount of spin density on the ortho hydrogen as a hyperconjugative mechanism places on each of the ortho methyl hydrogens.[11]

Protons in the interannular ring do not interact with unpaired spin. Yet, polar substituent effects are conducted through the metallocene ring with facility. In fact, the methyl hyperfine splitting constants of ferrocenyl methyl semidiones (Figure 2A) are as sensitive to 1′ substituents as phenyl methyl semidiones (Figure 2B) are to meta substituents; the ρ value for the plot of meta CH_3, Br, H, and CN values *vs.* $a_H^{CH_3}$ for both radical series are identical. These results indicate that the interannular substituent effects are primarily inductive in nature and that inductive effects are rather efficiently transferred between metallocene rings. Fig-

(9) M. Rosenblum, "Chemistry of the Iron Group Metallocenes," Wiley, New York, N. Y., 1965.

(10) The decrease in the magnitude of the 2-hydrogen splitting constants is a result of a time-averaged decrease in the C–H bond–semidione π system angle.

(11) For a discussion of spin delocalization mechanisms, see P. B. Ayscough, "Electron Spin Resonance in Chemistry," Methuen and Co., London, 1967, p 74.

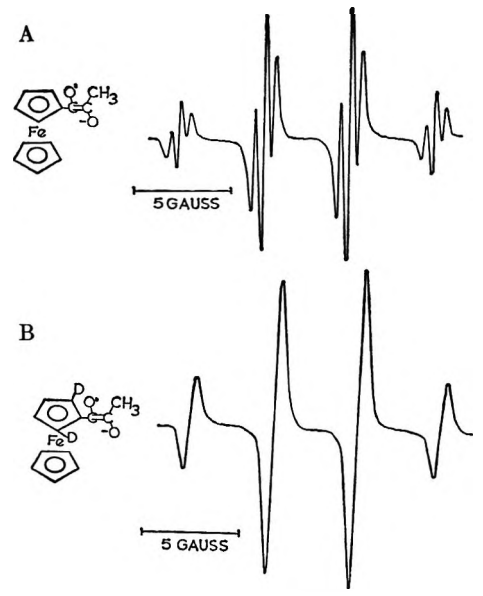


Figure 1.—Esr spectrum resulting from the oxidation of ketones 2 (A) and 2′ (B) in Table I.

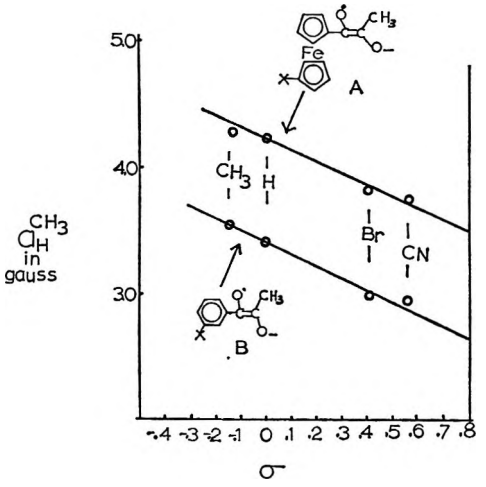


Figure 2.—A: Plot of methyl hyperfine splitting constants of methyl 1′-substituted ferrocenyl semidione *vs.* σ_m value of the interannular substituent. B: The corresponding plot for meta-substituted phenyl methyl semidiones. The latter data taken from a study by E. T. Strom, *J. Amer. Chem. Soc.*, 88, 2065 (1966).

ure 3 illustrates excellent correlation between the relative rates of solvolysis of 1′-substituted methyl ferrocenyl carbinyl acetates[12] and the hyperfine splitting constants of methyl 1′-substituted ferrocenyl semidiones. The least-squares analysis shows a correlation coefficient of 0.9906 and standard deviation of 0.19. Statistical analysis of the solvolysis data by Hall, Hill, and Richards[13] showed the best agreement when the rate data was plotted against inductive parameters σ_p^0 and σ_m^0 and they proposed an inductive mechanism in which resonance effects are not effectively transmitted by ring–metal bonds.[14]

The ferrocene and ruthenocene nuclei are remarkably ineffective in delocalizing unpaired spin. The cyman-

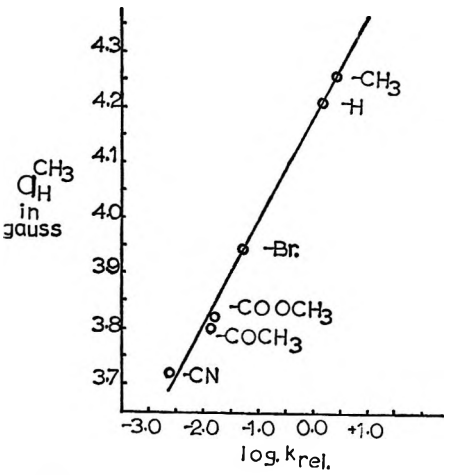


Figure 3.—Methyl hyperfine splitting constants of methyl 1′-substituted ferrocenyl semidiones *vs.* the relative rates of solvolysis of 1′-substituted methyl ferrocenyl carbinyl acetates.

trene[15] nucleus is somewhat more efficient in delocalizing electron spin and this behavior most likely reflects in the differences in the electron availability of the cyclopentadienyl anion ligands. For example, ferrocene > ruthenocene > cymantrene > benzene is the order of electrophilic attack; these nuclei have the opposite tendency to delocalize an odd electron. Electron availability facilitates electrophilic attack and appears to inhibit electron spin delocalization.

These semidiones have somewhat high g values. An interesting observation is that $g^1 < g^2$, an order opposite to that of the spin–orbit, LS, coupling constants for the metal ions involved (ζ Ru^{2+} = 1140 cm^{-1}, Fe^{2+} = 410 cm^{-1}). These results imply very little free electron density at the metal atom itself and this conclusion is supported by the absence of metal hyperfine splitting (Fe^{57}, spin = $^1/_2$, 2.245% natural abundance, Ru^{99}, spin = $^5/_2$, 12.81% natural abundance, or Ru^{101}, spin = $^5/_2$, 16.98% natural abundance). The metal apparently plays a more subtle role in its effect on the g value, perhaps by altering molecular orbital energy levels through $E1g$ (ring $E1g$–metal $d_{xy,yz}$) or $E2g$ (ring $E2g$–d_{xy,x^2-y^2}) ring–metal interaction so that the odd electron of ferrocene is in a higher energy orbital.[16] This difference in g value between entries 1 and 2 of Table I, as well as the interannular substituent effect on g values and hyperfine splitting constants, is clear evidence that the metallocene moiety remains intact during the oxidation procedure.

Spin density calculations of the Hückel–McLachlan type on π system I are in reasonable agreement with experimental values. In these calculations the effect of the metal ion is accommodated by altering the columbic integral of the cyclopentadienyl ring carbons to $\alpha = \alpha + h\beta$ where $h = -0.3$. This procedure makes the carbon atomic orbitals less electronegative and has the net effect of preventing spin delocalization into the cyclopentadienyl ring. The experimental values for the spin density, ρ, in position 1 and w were obtained by using the equation $a^H = Q\rho$. A Q value of 30 was chosen from the sum of the hydrogen hyperfine splitting constants of the cyclopentadiene radical. The experi-

(12) D. W. Hall, E. A. Hill, and J. H. Richards, *J. Amer. Chem. Soc.*, **90**, 4972 (1968).

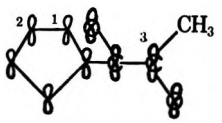
(13) The authors of ref 12 define an arbitrary parameter $(\sigma_m + 2\sigma_p)/2$ which fits better than σ_m^0 or σ_p^0. This parameter is not considered in the present work.

(14) Uv absorption data show very little interannular interaction. See ref 9, p 214.

(15) The ring protons of cymantrene (cyclopentadienylmanganese tricarbonyl) semidione have hyperfine splittings or 2.1 G ortho and 0.6 G meta; unpublished data from present authors.

(16) A. F. Stone, *Mol. Phys.*, **6**, 509 (1963).

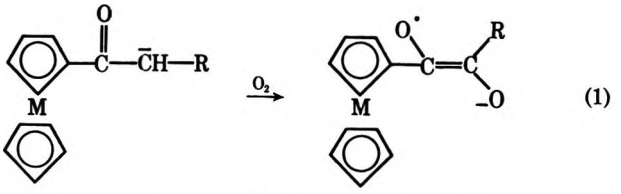
mental spin density at 3 was calculated from the methyl hyperfine splitting constant $a_H^{CH_3} = Q_{C-CH_3}\rho$ (carbon 3), where Q_{C-CH_3} equals 23. A more complete treatment of spin density calculations involving the cyclopentadienyl ring will appear elsewhere. It is also interesting to point out that the odd electron may occupy a ligand orbital which is not significantly involved in the metal ligand bonding.



I

Position	Calcd	Expt
1	0.015	0.0165
2	0.005	0.000
3	0.21	0.18

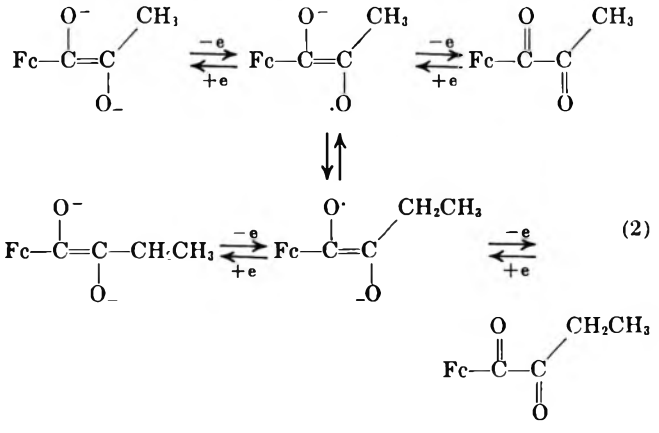
Oxidation Chemistry.—Steric and electronic factors control the rate of enolate anion oxidation (eq 1).



(1)

M	R	Relative rate of semidione formation
Fe	CH_3	21
Ru	CH_3	4.9
Fe	C_2H_5	2.45
Fe	$CH(CH_3)_2$	1

When equimolar concentrations of propionyl-, R = CH_3, and butyryl-, R = C_2H_5, ferrocene are oxidized competitively, the esr signal shows the relative intensity of the resulting semidiones to be 8.6:1, respectively. When the ketones are oxidized in base independently and then mixed in the absence of oxygen, the relative signal levels are approximately the same as before mixing. For example, the mixed signals with the R = CH_3 semidione are only twice the concentration as the R = Et semidione and this ratio is constant for the lifetime of the signal. These results indicate that equilibrium (eq 2) is not controlling the concentration



(2)

Fc = ferrocene

of the radicals and that the intensities of the signals observed represent the kinetic rate of semidione formation. The oxidation rate of propionylruthenocene is one-fourth that of the ferrocene analog. This difference is probably the result of ground-state stabilization of the enolate anion by the more electronegative

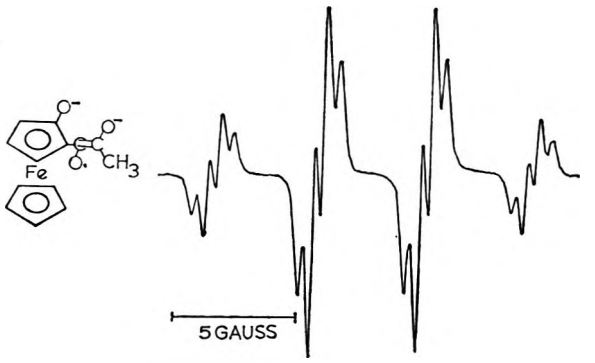


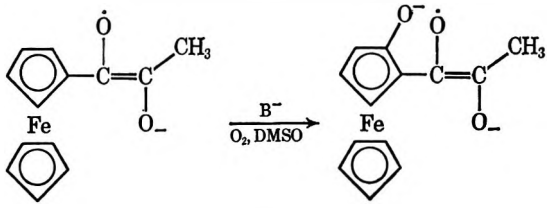
Figure 4.—Esr spectrum resulting from overoxidation of ferrocenyl methyl semidione.

Ru^{2+} ion. These reaction mechanisms are envisioned as the formation of equivalent amounts of each secondary anion in the large excess of very strong base followed by competition for a difficiency of oxygen. The detailed reaction mechanism is obscured by many competing reaction pathways.

The propionyl and butyryl moiety of 1,1′-propinylbutyrylferrocene (II) oxidize to the 1′-substituted semidiones III and IV in a 8.6 to 1 ratio as did the monosubstituted ketones. The former reaction requires a larger amount of potassium *tert*-butoxide and is also facilitated by the stronger base, cesium *tert*-butoxide. This effect of base implicates oxidation of the 1,1′ dianion V. The equilibrium VI ⇆ VII can be envisioned as lying in the direction of VI (Scheme I). In this regard, it is noteworthy that 1,1′-diferrocenyl ketones dialkylate[17] without monoalkylation, also implicating the dianion intermediate.

An excess of oxygen results in the disappearance of the original semidione and the appearance of a new paramagnetic species (Figure 4). These new paramagnetic species evidently result from ortho oxygenation of the metallocene ring. The data in Table II as-

TABLE II
HYPERFINE SPLITTING CONSTANTS OF RADICALS OBSERVED ON OVEROXIDATION

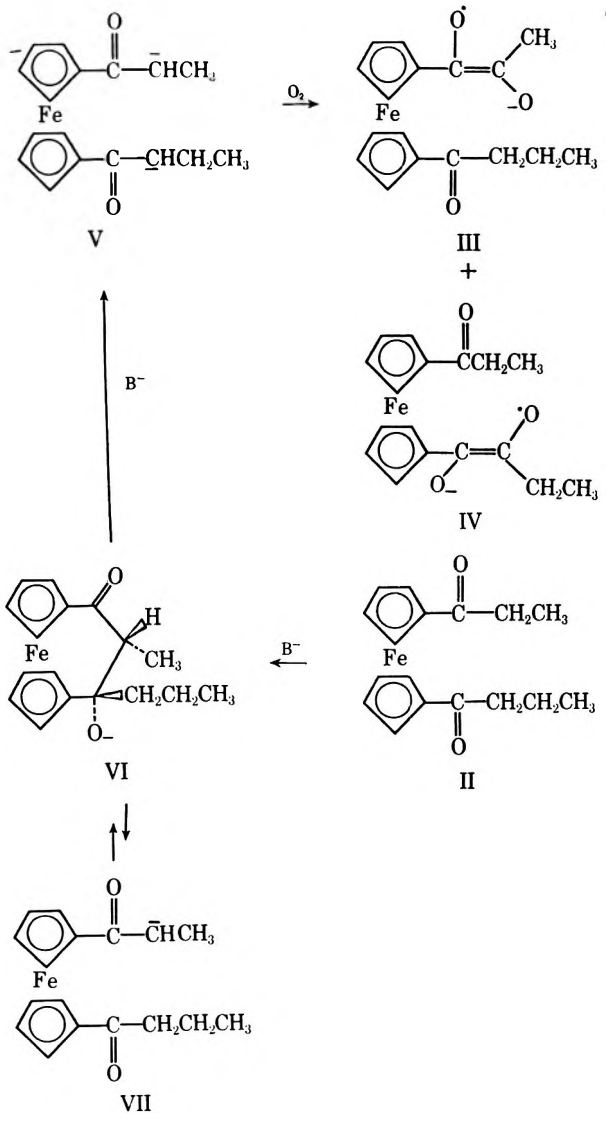


	a^H, gauss	g
1a → 1b	4.30 (3 H), 0.55 (3 H)	2.00644
2a → 2b	4.25 (3 H), 0.5 (3 H)	2.00708
3a → 3b	3.70 (2 H), 0.5 (3 H)	2.00708
4a → 4b	1.71 (2 H), 0.5 (3 H)	2.00708
2′a → 2′b	4.25 (3 H), 0.5 (2 H)	2.00708
2″a → 2″b	4.25 (3 H)	2.00708
11a → 11b	4.25 (3 H), 0.5 (4 H)	2.00740

sure that substitution is occuring in the ortho position and that the additional hydrogen hyperfine splitting originate in the metallocene ring. Homoannular electrophilic substitution of acetylferrocenes occurs exclusively in the ortho position[18] but the yield in the

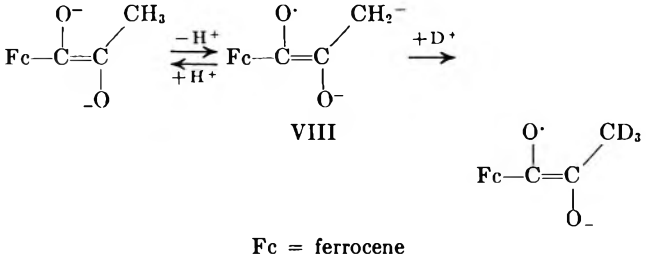
(17) C. R. Hauser and T. A. Mashburn, *J. Org. Chem.*, **26**, 1795 (1965).
(18) J. H. Richards and T. J. Curphey, *Chem. Ind.* (London), 1456 (1965).

Scheme I



reaction is extremely low. The overoxidation is a fairly efficient process and it is therefore reasonable to propose that the oxygen directly attacks what should be a more nucleophilic semidione as opposed to the ketone or α diketone.

Another unusual property of this class of semidione is the remarkably slow rate of hydrogen–deuterium exchange of the alkyl hydrogens α to the semidione when the oxidation is conducted in DMSO-d_6. This slow exchange rate is an indication that exchange is occurring from the dianion intermediate VIII. The powerful

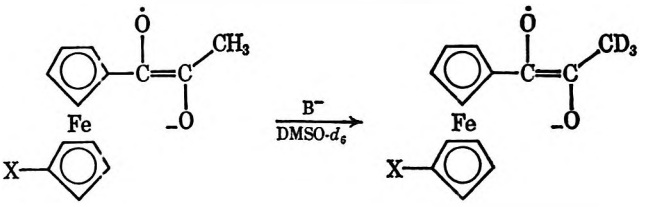


Fc = ferrocene

electron-supplying property of the metallocene ring also serves to retard the formation of the dianion. Table III list the times for complete H → D exchange. In general, the times of exchange are not affected by the transannular substituent unless the substituent is a ketone, in which case the rate of exchange is substantially increased as in entries of 3, 4, and 6 (Table III). Interannular stabilization of the dianion IX is most likely responsible for this effect. The protons α to the semidione in entry 7 and 8 of Table III were, as expected, much slower to exchange because the exchange respectively requires the formation of a secondary and a tertiary anion.

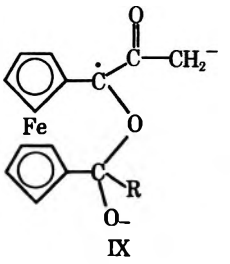
Table III

Hydrogen–Deuterium Exchange



X	Time for complete exchange, min
1. H	40 ± 5
2. p-C_6H_4Cl	40 ± 5
3. $COCH_2CH_2CH_3$	15 ± 5
4. $COC(CH_3)_3$	15 ± 5
5. CN	40 ± 5
6. Adamantyl ketone	15 ± 5
7.[a] H, $CH_2CH_3 \rightarrow CD_2CH_3$	10 hr
8.[a] H, $CH(CH_3)_2 \rightarrow CD(CH_3)_2$	72 hr

[a] Entries 7 and 8 represent the times for complete exchange of the α protons when the methyl group adjacent to the semidione is replaced by ethyl and isopropyl, respectively.



IX

Experimental Section

Esr Spectra.—The esr spectra were obtained on a Varian 4502 Model spectrometer with field dial control.

General Procedure for the Preparation of the Semidione.—To 10–15 mg of the ferrocenyl ketone in one side of an H cell was added 0.9 cc of dry DMSO; to a 3–4 molar excess of potassium *tert*-butoxide in the other half of the H cell was added 0.5 cc of dry DMSO. After thoroughly degassing both the solutions with N_2 (5 min), the sealed H cell was inverted and the solutions were thoroughly mixed. Unstoppering the H cell for a second allowed sufficient oxygen to enter to form the semidione. The procedure has previously been described.[19]

General Procedure for the Mixing of Semidione Solution.—The propionyl and butyryl semidiones were each prepared as described above in individual H cells and their approximate relative radical concentration was determined by instrumental settings. One of the radical-containing solutions was transferred to the other cell by means of a hypodermic syringe in a dry bag filled with nitrogen. The esr spectrum was observed after thorough mixing.

General Procedure for Hydrogen–Deuterium Exchange.—The semidione was prepared in the usual manner except that DMSO-d_6 (99.9%) was used in place of ordinary DMSO. The esr spectra was monitored as a function of time where t_0 was recorded at the addition of oxygen.

(19) G. A. Russell, E. G. Jansen, and E. T. Strom, *J. Amer. Chem. Soc.* **86**, 1807 (1964).

Propionylruthenocene (1).—To 3.0 g (0.023 mol) of anhydrous $AlCl_3$ in 75 ml of dry CH_2Cl_2 ($MgSO_4$) was added dropwise, with stirring, under N_2, 2.32 g (0.010 mol) of ruthenocene and 1.30 g (0.010 mol) of propionic anhydride. After refluxing for 3 hr the solution was hydrolyzed with H_2O and washed with water, and the layers were separated. The combined organic layer and the ether extract of the aqueous layer were dried ($MgSO_4$), concentrated to an oil, and chromatographed on alumina. Elution with 10% ether in Skelly B produced two bands. The first band (pale yellow) was starting material. The second band (yellow) contained 1.18 g (41%) of 1: mp 70–71°; nmr ($CDCl_3$) δ 1.14 (t, 3, CH_3), 2.63 (d, 2, CH_3), 4.57 (s, 5, Rc), 4.65 (t, 2, Rc), and 5.11 (t, 2, Rc).

Anal. Calcd for $C_{13}H_{14}ORu$: C, 54.36; H, 4.88. Found: C, 54.24; H, 4.95.

Propionylferrocene (2).—2 was prepared by the method of Rinehardt[20] in 50% yield: mp 37.5–38° (lit.[20] 38–39°); nmr (C_6D_6) δ 1.12 (t, 3, CH_3), 2.45 (m, 2, CH_2), 3.90 (s, 5, Fc), and 4.10 (t, 2, Fc).

Anal. Calcd for $C_{13}H_{14}OFe$: C, 64.46; H, 5.78. Found: C, 64.20; H, 6.59.

2,5-Dideuteriopropionylferrocene (2′).—2′ was prepared by the method of Rausch[21] employing ethyllithium instead of methyllithium in one step of the reaction: mp 36° (lit.[20] 38–39°): nmr ($CDCl_3$) δ 1.20 (t, 3, CH_3), 2.74 (m, 2, CH_2), 4.17 (s, 5, Fc), and 4.48 (s, 2, Fc); *m/e* 244, 243, and 242 show greater than 96% deuterium incorporation.

Propionylferrocene-d_9 (2″).—Ferrocene-d_{10} (1.0 g, 0.0051 mol), as prepared by the method of Pavlik,[22] 0.72 g (0.0065 mol) of $AlCl_3$, and 0.60 g (0.0046 mol) of propionic anhydride were reacted for 4 hr in the manner and under the conditions described for 4. Subsequent chromatography on silica gel produced two bands when eluting with Skelly B. The second band (orange) contained 0.5 g (38.5%) of 2″: mp 38° (lit.[20] 38–39°); nmr ($CDCl_3$) δ 1.20 (t, 3, CH_3) and 2.74 (m, 2, CH_2); *m/e* 251 to 242 showed greater than 96% d_9 incorporation.

Butyrylferrocene (3).—3 was prepared by the method of Schlogl[23] in 75% yield: mp 34–35° [lit.[23] bp 144–145° (1.5 mm)]; nmr ($CDCl_3$) 1.00 (t, 3, CH_2), 1.76 (m, 2, CH_2CH_3), 2.68 (t, 2, $COCH_2$), 4.17 (s, 5, Fe), 4.47 (t, 2, Fc), and 4.77 (t, 2, Fc).

Anal. Calcd for $C_{14}H_{16}OFe$: C, 65.63; H, 6.25. Found: C, 65.58; H, 6.35.

3-Methylbutyrylferrocene (4).—$AlCl_3$ (7.8 g, 0.0600 mol), 10.0 g (0535 mol) of ferrocene, and 5.95 g (0.0536 mol) of 3-methylbutyryl chloride were reacted and worked up according to the method described for 1 except that the reaction mixture was not refluxed. Chromatography on alumina produced two bands when eluting with 10% ether in Skelly B. Of the two bands obtained, the first band (yellow) contained ferrocene. The second band (red) contained 7.86 g (56.2%) of 4: mp 55–56°; nmr ($CDCl_3$) δ 1.0 (s, 6, CH_3), 2.28 (m, 1, CH), 2.58 (d, 2, CH_2), 4.17 (s, 5, Fc), 4.47 (t, 2, Fc), and 4.77 (t, 2, Fc).

Anal. Calcd for $C_{15}H_{18}OFe$: C, 66.67; H, 6.67. Found: C, 66.53; H, 6.69.

4-Methylvalerylferrocene (5).—$AlCl_3$ (7.2 g, 0.0540 mol), 10 g (0.0535 mol) of ferrocene, and 7.2 g (0.0537 mol) of 4-methylvaleryl chloride were reacted and worked up as in the preparation of 4. Chromatography on silica gel produced two bands when eluting with 10% ether in Skelly B. The first band (yellow) contained ferrocene and the second band (red) contained 10.17 g (66.7%) of 5: mp 33–34°; nmr ($CDCl_3$) δ 0.97 (d, 6, CH_3), 1.55 (t, 2, CH_2), 2.06 (m, 1, CH), 2.69 (t, 2, $COCH_2$), 4.17 (s, 5, Fc), 4.47 (t, 2, Fc), and 4.77 (t, 2, Fc).

Anal. Calcd for $C_{16}H_{20}OFe$: C, 67.61; H, 7.04 Found: C, 67.60; H, 7.18.

Benzylferrocenyl Ketone (6).—6 was prepared according to the method of Dabard[24] in 78% yield: mp 129–130° (lit.[24] 130°); nmr ($CDCl_3$) δ 3.98 (s, 2, CH_2), 4.00 (s, 5, Fc), 4.50 (t, 2, Fc), 4.83 (t, 2, Fc), and 7.33 (s, 5, Ph).

Anal. Calcd for $C_{18}H_{16}O$ Fe: C, 7105; H, 5.26. Found: C, 69.96; H, 5.35.

1-Propionyl-2-acetylferrocene (7) **and 1-Propionyl-1-acetylferrocene** (22).—22 was prepared by the method of Furdik[25] in 62.8%: mp 58.5–59° (lit.[25] 54–55°); nmr ($CDCl_3$) δ 1.19 (t, 3, CH_2CH_3), 2.35 (s, 3, $COCH_3$), 2.70 (m, 2, CH_2), 4.49 (t, 4, Fc), and 4.77 (m, 4 Fc). Also obtained by chromatography (on silica gel) was 7 in 5.3% yield when eluting with 25% ether in Skelly B: mp 46°; nmr ($CDCl_3$) δ 1.17 (t, 3, CH_2CH_3), 2.47 (s, 3, $COCH_3$), 2.86 (m, 2, CH_2), 4.25 (s, 5, Fc), 4.58 (t, 1, Fc), and 4.88 (d, 2, Fc).

Anal. Calcd for $C_{15}H_{16}O_2Fe$ (22): C, 63.38; H, 5.63. Found: C, 63.31; H, 5.69.

Anal. Calcd for $C_{15}H_{16}O_2Fe$ (7): C, 63.38; H, 5.63. Found: C, 63.28; H, 5.71.

1,1′-Di-*n*-butyl-2-propionylferrocene (8) **and 1,1′-Di-*n*-butyl-3-propionylferrocene** (11).—$AlCl_3$ (8.0 g, 0.0602 mol), 10 g (0.0334 mol) of 1,1′-di-*n*-butylferrocene, and 5 g (0.0385 mol) of propionic anhydride were reacted for 15 hr according to the preparation of 4. Chromatography on silica gel produced four bands when eluting with Skelly B. The first band (yellow) contained 0.5 g of starting material. The second band (orange) contained 2.0 g (16.8%) of 8: bp 170–172° (0.3 mm); nmr ($CDCl_3$) δ 1.17 (m, 17, $CH_2CH_2CH_3$, $COCH_2CH_3$), 2.22 (t, 4, Fc CH_2), 2.73 (m, 2, $COCH_2$), 3.96 (s, 4, Fc), 4.25 (m, 2, Fc), and 4.54 (m, 1, Fc). The third band contained 7.7 g (64.8%) of 11: bp 177–179° (0.3 mm); nmr ($CDCl_3$) 1.17 (m, 17, $CH_2CH_2CH_3$, $COCH_2CH_3$), 2.23 (t, 4 H, Fc CH_2), 2.68 (m, 2, $COCH_2$), 3.95 (s, 4, Fc), 4.28 (m, 1 H, Fc), and 4.58 (m, 2 H, Fc). The fourth band (red) was not characterized.

Anal. Calcd for $C_{21}H_{30}OFe$ (8): C, 71.19; H, 8.47. Found: C, 71.15; H, 8.63.

Anal. Calcd for $C_{21}H_{30}OFe$ (11): C, 71.19; H, 8.47. Found: C, 71.08; H, 8.62.

1,1′-Dimethyl-2-propionylferrocene (9) **and 1,1′-Dimethyl-3-propionylferrocene** (12).—$AlCl_3$ (7.14 g, 0.0536 mol), 7.12 g (0.0331 mol) of 1,1′-dimethylferrocene, and 4.0 g (0.0307 mol) of propionic anhydride were reacted for 15 hr as in the preparation of 4. Chromatography on silica gel, eluting with 10% ether in Skelly B, produced three bands. The second band (orange) contained 1.62 g (18.1%) of 9: bp 138–141° (0.3 mm); nmr ($CDCl_3$) δ 1.17 (t, 3, CH_2CH_3), 1.87 (s, 3, Fc CH_3), 2.27 (s, 3, Fc CH_3), 2.73 (m, 2, $COCH_2$), 3.95 (s, 4, Fc), 4.27 (m, 2, Fc), and 4.54 (m, 1, Fc). The third band (red) contained 3.92 g (43.7%): bp 140–144° (0.3 mm); nmr ($CDCl_3$) δ 1.18 (t, 3, CH_2CH_3), 1.88 (s, 3, Fc CH_3), 2.02 (s, 3, Fc CH_3), 2.70 (m, 2, $COCH_2$), 3.96 (s, 4, Fc), 4.30 (m, 1, Fc), and 4.60 (m, 2, Fc).

Anal. Calcd for $C_{15}H_{19}OFe$ (9): C, 66.42; H, 7.01. Found: C, 66.25; H, 7.05.

Anal. Calcd for $C_{15}H_{19}OFe$ (12): C, 66.42; H, 7.01. Found: C, 66.37; H, 7.09.

1-Propionyl-2-*p*-chlorophenylferrocene (10), **1-Propionyl-3-*p*-chlorophenylferrocene** (13), **and 1-Propionyl-1′-*p*-chlorophenylferrocene** (15).—*p*-Chloroferrocene (4.20 g, 0.0141 mol) as prepared by the method of Weinmayer,[26] 2.5 g (0.0187 mol) of $AlCl_3$, and 2.0 g (0.0153 mol) of propionic anhydride were reacted for 4.5 hr in the manner and under the conditions described for 4.

After the starting material was separated by chromatography on silica gel when eluting with Skelly B, 15 was separated from the reaction mixture by selective recrystallization: 1.51 g (30.2%); mp 102–103°; nmr ($CDCl_3$) δ 1.07 (t, 3, CH_3), 2.47 (m, 2, CH_2), 4.33 (t, 4, Fc), 4.62 (m, 4, Fc), and 7.28 (s, 4, Ph). The remaining material was rechromatographed on silica gel eluting with 7% benzene in cyclohexane. Two major bands developed. The first band (orange) contained 0.93 g (18.6%) of 13: mp 113°; nmr ($CDCl_3$) 1.22 (t, 3, CH_3), 2.77 (m, 2, CH_2), 4.04 (s, 5, Fc), 4.90 (d, 2, Fc), 5.23 (m, 1, Fc), and 7.34 (m, 4, Ph). The second band (yellow) contained 0.77 g (15.4%) of 10: mp 103°; nmr ($CDCl_3$) δ 1.17 (t, 3, CH_3), 2.74 (m, 2, CH_2), 4.20 (s, 5, Fc), 4.60 (m, 2, Fc), 4.84 (m, 1, Fc), and 7.40 (m, 4, Ph).

Anal. Calcd for $C_{19}H_{17}OClFe$ (15): C, 64.59; H, 4.81. Found: C, 64.42; H, 4.92.

Anal. Calcd for $C_{19}H_{17}OClFe$ (10): C, 64.59; H, 4.81. Found: C, 64.61; H, 4.88.

Anal. Calcd for $C_{19}H_{17}OClFe$ (13): C, 64.59; H, 4.81. Found: C, 64.45; H, 4.92.

1-Propionyl-1′-*tert*-butylferrocene (14).—*tert*-Butylferrocene (2.3 g, 0.0093 mol), as prepared by the method of Neuse,[27] 1.25

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(27) E. W. Neuse and D. S. Trifan, *ibid.*, **84**, 1850 (1962).

g (0.0094 mol) of $AlCl_3$, and 1.20 g (0.0092 mol) of propionic anhydride were reacted according to the preparation of **4**. Chromatography on alumina produced four bands. The second band (orange) contained 0.6 g (22.0%) of **14**: nmr ($CDCl_3$) δ 1.17 (t, 3, CH_2CH_3), 1.22 (s, 9, $C(CH_3)_3$), 2.70 (m, 2, CH_2), 4.05 (m, 2, Fc), 4.15 (d, 2, Fc), 4.47 (m, 2, CH_2), 4.05 (m, 2, Fc), 4.15 (d, 2, Fc), 4.47 (m, 2, Fc), and 4.75 (m, 2, Fc).

Anal. Calcd for $C_{17}H_{22}OFe$: C, 73.28; H, 7.38. Found: C, 73.20; H, 7.47.

1-Propionyl-1′-bromoferrocene (16).—Bromoferrocene (2.44 g, 0.0067 mol), as prepared by the method of Fish,[28] 0.75 g (0.0057 mol) of propionic anhydride, and 0.92 g (0.0069 mol) of $AlCl_3$ were reacted as in the preparation of **4** but at 0°. Chromatography on silica gel produced two bands when eluting with Skelly B. The first band (yellow) contained 1.45 g of bromoferrocene (59.5%) and the second band (orange) contained 0.61 g (20.9%) of **16**: mp 31°; nmr ($CDCl_3$) δ 1.19 (t, 3, CH_3), 2.78 (m, 2, CH_2), 4.12 (t, 2, Fc), 4.41 (t, 2, Fc), 4.52 (t, 2, Fc), and 4.82 (t, 2, Fc).

Anal. Calcd for $C_{13}H_{13}OBrFe$: C, 48.60; H, 5.04. Found: C, 48.52; H, 4.13.

1-Propionyl-1′-carboadamantylferrocene (17).—To 20 g (0.1504 mol) of $AlCl_3$ in 150 ml of dry CH_2Cl_2 ($MgSO_4$) was added with stirring, under N_2, 9 g (0.0481 mol) of ferrocene and 11 g (0.0554 mol) of adamantanecarboxyl chloride in 300 ml of dry CH_2Cl_2. The solution was refluxed for 30 hr. After the usual work-up, the oil was chromatographed on alumina and three bands were obtained. The second band (orange) was brought down with CH_2Cl_2 to yield 7.0 g (38.4%) of adamantylferrocenyl ketone: mp 147–148°; nmr ($CDCl_3$) δ 1.80 (m, 5, Ad), 4.18 (s, 5, Fc), and 4.90 (t, 2, Fc).

Adamantylferrocenyl ketone (1.7 g, 0.0049 mol), 4.5 g (0.0338 mol) of $AlCl_3$, and 3.5 g (0.0269 mol) of propionic anhydride were allowed to react for 4.5 hr in the manner and under the conditions described for **4**. Chromatography on alumina produced two bands when eluting with 25% ether in Skelly B. The second band (orange brown) was brought down with ether and contained 1.4 g (71%) of **17**: mp 89°; nmr ($CDCl_3$) δ 1.17 (t, 3, CH_3), 1.75 (m, 5, Ad), 2.00 (s, 10, Ad), 2.60 (m, 2, CH_2), 4.43 (m, 4, Fc), 4.77 (t, 2, Fc), and 4.87 (t, 2, Fc).

Anal. Calcd for $C_{24}H_{28}O_2Fe$: C, 71.29; H, 6.93. Found: C, 71.17; H, 7.02.

1-Propionyl-1′-pivalylferrocene (18).—Pivalylferrocene (1.70 g, 0.0062 mol), as prepared by the method of Stephenson,[29] 4.5 g (0.0338 mol) of $AlCl_3$, and 3.5 g (0.0269 mol) of propionic anhydride were reacted for 4.5 hr in the manner and under the conditions prescribed for **4**. Chromatography on alumina produced two bands when eluting with 10% ether in Skelly B. The second band (red) contained 1.67 g (81.4%) of **18**: mp 32°; nmr ($CDCl_3$) δ 1.20 (t, 3, CH_2CH_3), 1.32 (s, 9, $C(CH_3)_3$), 2.75 (m, 2, CH_2), 4.48 (t, 4, Fc), 4.78 (t, 2, Fc), and 4.84 (t, 2, Fc).

Anal. Calcd for $C_{18}H_{22}O_2Fe$: C, 66.26; H, 6.75. Found: C, 6619; H, 6.77.

1-Propionyl-1′-3-methylbutyrylferrocene (19).—**4** (3.65 g, 0.0135 mol), 8.1 g (0.0609 mol) of $AlCl_3$, and 3.83 g (0.0294 mol) of propionic anhydride were reacted for 4.5 hr in the manner and under the conditions prescribed for **4**. Chromatography on silica gel produced two bands when eluting with 10% ether in Skelly B. The one band which developed yielded 3.52 g (79.5%) of **19**: mp 42°; bp 193–194° (0.3 mm); nmr ($CDCl_3$) δ 1.00 (d, 5, $CH(CH_3)_2$), 1.19 (t, 3, CH_2CH_3), 2.25 (m, 1, CH), 2.54 (d, 2, CH_2CH), 2.70 (m, 2, CH_2CH_3), 4.47 (m, 4, Fc), and 4.77 (m, 4, Fc).

Anal. Calcd for $C_{18}H_{22}O_2Fe$: C, 66.26; H, 6.75. Found: C, 66.18; H, 6.79.

1-Propionyl-1′-carbomethoxyferrocene (20).—**20** was prepared by the method of Perevalova:[30] mp 64° (lit. 64–65°); nmr ($CDCl_3$) δ 1.18 (t, 3, CH_2CH_3), 2.73 (m, 2, CH_2), 3.80 (s, 3, OCH_3), 4.38 (t, 2, Fc), 4.48 (t, 2, Fc), and 4.79 (t, 4, Fc).

Anal. Calcd for $C_{15}H_{16}O_3Fe$: C, 60.00; H, 5.33. Found: C, 60.06; H, 5.44.

1-Propionyl-1-butyrylferrocene (21).—**3** (2.35 g, 0.0087 mol), 5.41 g, 0.0407 mol) of $AlCl_3$, and 2.50 g (0.0324 mol) of propionic anhydride were reacted for 4.5 hr in the manner and under the conditions prescribed for **4**. Chromatography on silica gel produced two bands when eluting with 10% ether in Skelly B. The second band (red) contained 2.0 g (73.2%) of **21**: mp 39.5°; bp 180–182° (0.3 mm); nmr ($CDCl_3$) δ 1.00 (t, 3, $CH_2CH_2CH_3$), 1.17 (t, 3, $COCH_2CH_3$), 1.73 (m, 2, $CH_2CH_2CH_3$), 2.63 (t, 2, $COCH_2CH_2$), 2.69 (m, 2, $COCH_2CH_3$), 4.45 (t, 4, Fc), and 4.76 (t, 4, Fc).

Anal. Calcd for $C_{17}H_{20}O_2Fe$: C, 65.38; H, 6.41. Found: C, 65.19; H, 6.50.

1-Propionyl-1′-*p*-toluylferrocene (23).—*p*-Toluylferrocene (0.85 g, 0.0028 mol), as prepared by the method of Dabard,[24] 3.0 g (0.0226 mol) of $AlCl_3$, and 1.5 g (0.0115 mol) of propionic anhydride were reacted for 4.0 hr in the manner and under the conditions prescribed for **4**. Chromatography on silica gel produced a single band, when eluting with 10% ether in Skelly B, which yielded 0.91 g (90%) of **23**: mp 103°; nmr ($CDCl_3$) δ 1.10 (t, 3, CH_2CH_3), 2.43 (s, 5, Ph CH_3), 2.60 (m, 2, CH_2), 4.46 (t, 2, Fc), 4.53 (t, 2, Fc), 4.75 (t, 2, Fc), 4.89 (t, 2, Fc), and 7.51 (m, 4, Ph).

Anal. Calcd for $C_{21}H_{20}O_2Fe$: C, 70.00; H, 5.56. Found: C, 69.88; H, 5.69.

1-Propionyl-1′-cyanoferrocene (24).—Cyanoferrocene (0.85 g, 0.0040 mol), as prepared by the method of Broadhead,[31] 2.0 g (0.0150 mol) of $AlCl_3$, and 1.56 g (0.0120 mol) of propionic anhydride were reacted for 4 hr in the manner and under the conditions prescribed for **4**. Chromatography on alumina produced two bands when eluting with 10% ether in Skelly B. The second band (orange) contained 1.00 g (93.3%) of **24**: mp 53°; nmr ($CDCl_3$) δ 1.20 (t, 3, CH_3), 2.78 (m, 2, CH_2), 4.40 (t, 4, Fc), and 4.93 (t, 2, Fc); ir (neat) 2220 cm^{-1} (C≡N).

Anal. Calcd for $C_{14}H_{13}ONFe$: C, 62.72; H, 4.87; N, 5.24. Found: C, 62.81; H, 4.92; N, 5.36.

Registry No.—**1**, 12512-44-6; **1a**, 12512-42-4; **1b**, 12512-39-9; **2**, 1271-79-0; **2a**, 12512-41-3; **2b**, 12512-38-8; **2′**, 12512-40-2; **2′a**, 12512-36-6; **2′b**, 12512-35-5; **2″**, 12512-34-4; **2″a**, 12512-33-3; **2″b**, 12512-32-2; **3**, 1271-94-9; **3a**, 12512-49-1; **3b**, 12512-48-0; **4**, 12512-59-3; **4a**, 12512-57-1; **4b**, 12512-53-7; **5**, 12512-63-9; **5a**, 12512-62-8; **6**, 12512-69-5; **6a**, 12512-68-4; **7**, 12512-56-0; **7a**, 12512-51-5; **8**, 12512-86-6; **8a**, 12512-85-5; **9**, 12512-60-6; **9a**, 12512-55-9; **10**, 12512-77-5; **10a**, 12512-76-4; **11**, 12512-87-7; **11a**, 12512-84-4; **11b**, 12512-83-3; **12**, 12512-61-7; **12a**, 12512-58-2; **13**, 12512-78-6; **13a**, 12512-75-3; **14**, 12512-67-3; **14a**, 12512-66-2; **15**, 12512-79-7; **15a**, 12512-74-2; **16**, 12512-43-5; **16a**, 12512-37-7; **17**, 12512-89-9; **17a**, 12512-88-8; **18**, 12512-72-0; **18a**, 12512-70-8; **19**, 12512-73-1; **19a**, 12512-71-9; **20**, 1272-28-2; **20a**, 12512-52-6; **21**, 12512-65-1; **21a**, 12512-64-0; **22**, 12512-54-8; **22a**, 12512-50-4; **23**, 12512-81-1: **23a**, 12512-80-0; **24**, 12512-47-9; **24a**, 12512-46-8; adamantylferrocene ketone, 12512-82-2.

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(30) E. G. Perevalova, *et al.*, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1901 (1964); *Chem. Abstr.*, **62**, 2792 (1965).

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The Coupling Reaction of Phenyllithium with Allylic Chlorides. The Influence of Methyl Substituents on the Distribution of Products[1a,b]

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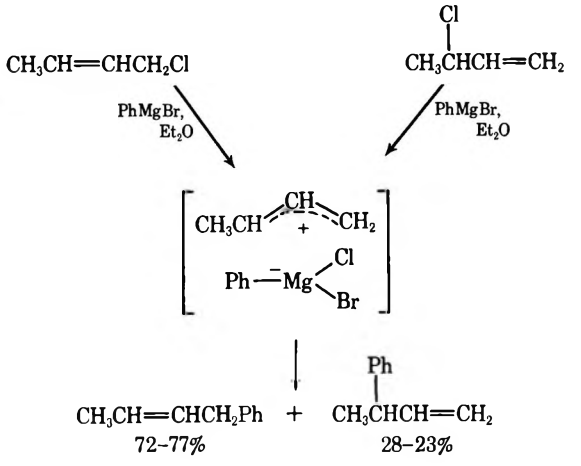
The reaction of phenyllithium with each of the possible mono- and dimethyl-substituted allylic chlorides is reported. Included are chlorides in which the termini of the allylic system are made distinguishable by ^2H or ^{14}C labels [3-chloro-2-methyl-1-propene and 4-chloro-*trans*- (or *cis*-) -2-pentene], although numerous attempts to prepare the latter compound exclusively tagged at one position were unsuccessful. The distribution of coupling products from the reaction with phenyllithium is discussed with respect to the influence of α-, β-, or γ-methyl substituents on the position of attack. The total preservation of double bond geometry when *trans*- or *cis*-1-chloro-2-butene and *trans*- or *cis*-1-chloro-2-methyl-2-butene undergo α attack is used to argue against previously proposed ion-pair and radical-pair mechanisms. The nonidentical product distributions from pairs of allylic isomers stand in contrast to earlier reports and are also most simply interpreted in terms of a concerted process.

Allylic halides couple with a wide variety of organometallic reagents, and several distinct mechanisms have been proposed. The first reasonable scheme was put forth by Wilson, Roberts, and Young[2] to explain the nearly identical distribution of products from reaction of phenylmagnesium bromide with either α- or γ-methylallyl chloride. They suggested that coordination of magnesium with chlorine sufficiently weakens the C–Cl bond that an ion-pair intermediate with almost no memory of its origin is formed; this intermediate then collapses to the two products (Scheme I). Reac-

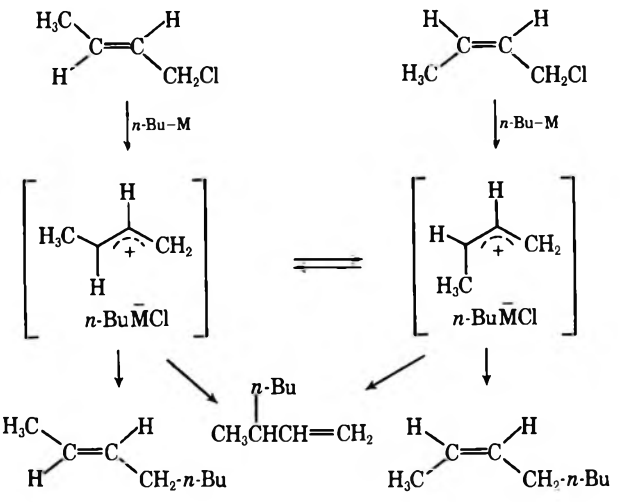
SCHEME I



tion of the same two chlorides with phenyllithium in ether similarly was reported to produce identical product mixtures consisting of about 90% crotylbenzene and 10% α-methylallylbenzene; the ion-pair mechanism was, again, invoked.[3]

More recently, Czernecki, *et al.*,[4] presented a detailed study of the reactions of *cis*- and *trans*-crotyl chloride and α-methylallyl chloride with *n*-butyllithium, *n*-butylsodium, and *n*-, *sec*-, and *tert*-butylmagnesium bromide. They concluded that all of the organometallic reagents produce products by the same general mechanism: heterolysis of the C–Cl bond by coordination to the metal followed by collapse of the ion pair to products (Scheme II). Differences between

SCHEME II



the various reagents were attributed to a delicate interplay of two factors: the relative electrophilicity of the metal (increasing from sodium to lithium to magnesium) and the relative nucleophilicity of the butyl group (decreasing along this series). In particular, with Grignard reagents the ion-pair intermediate is presumed to be longer lived and capable of bond rotation, thereby allowing partial loss of double bond geometry in the products from *cis*- and *trans*-crotyl chloride; with the lithium and, especially, sodium reagents, more rapid collapse to products results in essentially no loss of double bond stereochemistry. Differences in product distributions from the three chlorides were also interpreted within this framework.

A variation of this ion-pair mechanism was offered by Wawzonek, *et al.*,[5] to account for the purported loss of double bond integrity in the products from *cis*- and *trans*-crotyl chloride with phenyllithium and phenylsodium. In their view, the ion pair can return to covalent chloride and, to the extent that α-methylallyl chloride is thus generated, both *cis*- and *trans*-crotylbenzene are expected (Scheme III). The rather high activation energy for rotation about the partial

(1) (a) A portion of this work has appeared in preliminary form: R. M. Magid and R. D. Gandour, *J. Org. Chem.*, **35**, 269 (1970). (b) Partial support of this work by the Robert A. Welch Foundation is gratefully acknowledged, as is the assistance of the National Science Foundation in the purchase of a Varian Associates A-56/60A nmr spectrometer. (c) To whom inquiries should be addressed at the Department of Chemistry, The University of Tennessee, Knoxville, Tenn. 37916.

(2) K. W. Wilson, J. D. Roberts, and W. G. Young, *J. Amer. Chem. Soc.*, **71**, 2019 (1949).

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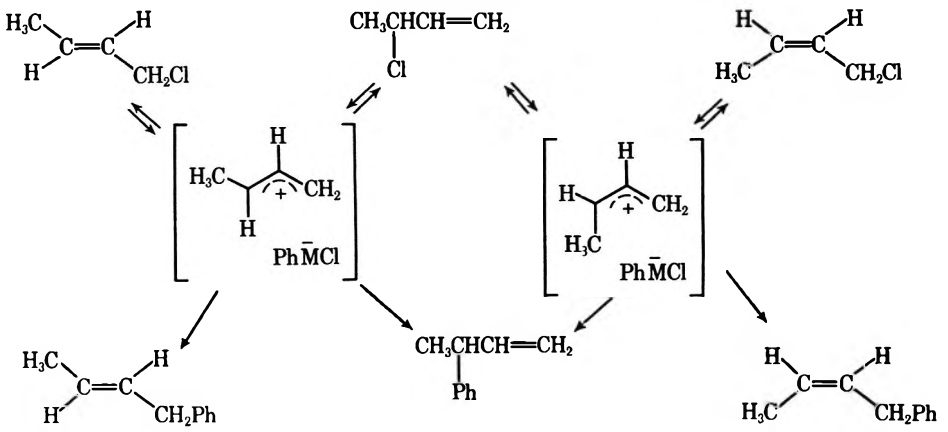
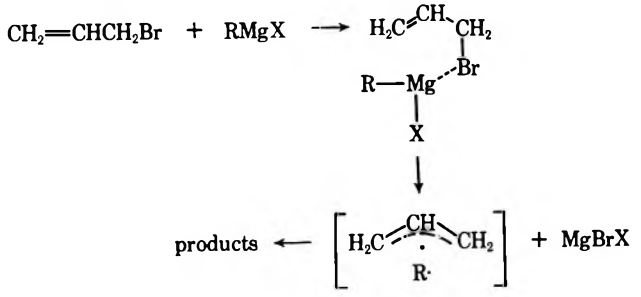
SCHEME III



double bond of long-lived allylic cations in strongly ionizing media[6] would probably argue against Scheme II and for this variation.

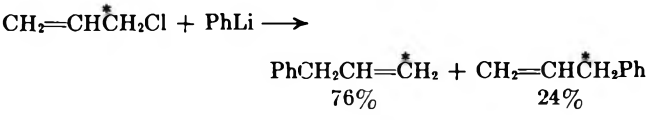
A distinctly different sort of mechanism was suggested by Gough and Dixon[7] for the coupling of allyl bromide with Grignard reagents. Based upon relative rate data, isolation and characterization of several minor products, and detection of an esr signal, a radical-pair intermediate was put forth (Scheme IV).

SCHEME IV



Certainly, organolithium reagents also exhibit radical character in many of their reactions,[8-10] thereby making the Gough–Dixon mechanism a likely possibility for their interaction with allylic halides. It should be noted, however, that *cis*- and *trans*-crotyl radicals have been studied by esr techniques which show that they undergo absolutely no interconversion at or below 0° in hydrocarbon solvent.[11]

Thus, all of the suggested mechanisms have invoked an intermediate (ionic or radical) which, by separation from the leaving group,[2,3] bond rotation,[4] or internal return,[5] has forgotten the identity of its precursor to some extent. In direct contrast to these proposals, the reaction of phenyllithium with the parent compound, allyl chloride, gives no evidence requiring the intervention of an intermediate. Allyl chloride, labeled at the α position with either ^2H or ^{14}C, produces allylbenzene, analysis of which shows that the majority of coupling has occurred at the γ position.[12] Clearly, a



truly symmetrical intermediate (ionic or radical) is not involved here, nor can one account for the product distribution by secondary isotope effects.[12]

In an effort to clarify the mechanistic details of the coupling reaction and to reconcile the allyl chloride results with those that appear to demand an intermediate, we now report on the influence of variously situated methyl substituents on the relative amounts of phenyllithium attack at the α and γ carbons. In the following paper, we describe the stereochemistry of the reaction.

Results

We have investigated the distribution of coupling products from phenyllithium with each of the possible mono- and dimethyl-substituted allylic chlorides (Chart I). Each of these materials is either commercially available or has been reported in the literature. In practice, however, none of these compounds (whether purchased or prepared) was sufficiently pure for use in the coupling reaction. Because of this and the further fact that several of these chlorides tended to decompose and/or isomerize during storage, it was necessary to carefully purify each material (see Experimental Section) and to use it immediately.

Since chlorides **4**, **10**, and **11** are symmetrical in the sense that attack at either the α or γ carbon would yield the same product, it was necessary to distinguish the termini of the allylic system by a suitable isotopic label (Chart II). Monomethyl compound **4**-d_2 was

(6) (a) P. v. R. Schleyer, T. M. Su, M. Saunders, and J. C. Rosenfeld, *J. Amer. Chem. Soc.*, **91**, 5174 (1969); (b) J. M. Bollinger, J. M. Brinich, and G. A. Olah, *ibid.*, **92**, 4025 (1970).

(7) R. G. Gough and J. A. Dixon, *J. Org. Chem.*, **33**, 2148 (1968).

(8) Exchange and coupling reactions with alkyl halides: (a) C. G. Screttas and J. F. Eastham, *J. Amer. Chem. Soc.*, **88**, 5668 (1966); (b) H. R. Ward and R. G. Lawler, *ibid.*, **89**, 5518 (1967); (c) H. R. Ward, R. G. Lawler, and H. Y. Loken, *ibid.*, **90**, 7359 (1968); (d) H. R. Ward, R. G. Lawler, and R. A. Cooper, *ibid.*, **91**, 746 (1969); (e) A. R. Lepley, *ibid.*, **90**, 2710 (1968); *ibid.*, **91**, 749 (1969); *Chem. Commun.*, 64 (1969); (f) A. R. Lepley and R. L. Landau, *J. Amer. Chem. Soc.*, **91**, 748 (1969); (g) G. A. Russell and D. W. Lamson, *ibid.*, **91**, 3967 (1969); (h) F. Gerhart and G. Ostermann, *Tetrahedron Lett.*, 4705 (1969); (i) J. W. Rakshys, Jr., *Chem. Commun.*, 578 (1970).

(9) Additions to multiple bonds: (a) H. R. Ward, *J. Amer. Chem. Soc.*, **89**, 5517 (1967); (b) J. E. Mulvaney, S. Groen, L. J. Carr, Z. G. Gardlund, and S. L. Gardlund, *ibid.*, **91**, 388 (1969); (c) C. Blomberg and H. S. Mosher, *J. Organometal. Chem.*, **13**, 519 (1968); (d) J. K. Crandall and D. J. Keyton, *Tetrahedron Lett.*, 1653 (1969).

(10) Intramolecular rearrangements: (a) F. Gerhart, *ibid.*, 5061 (1969); (b) J. E. Baldwin, J. DeBernadis, and J. E. Patrick, *ibid.*, 353 (1970); (c) E. Grovenstein, Jr., and Y-M. Cheng, *Chem. Commun.*, 101 (1970).

(11) J. K. Kochi and P. J. Krusic, *J. Amer. Chem. Soc.*, **90**, 7157 (1968).

(12) (a) R. M. Magid and J. G. Welch, *ibid.*, **88**, 5681 (1966); (b) R. M. Magid and J. G. Welch, *ibid.*, **90**, 5211 (1968).

CHART I

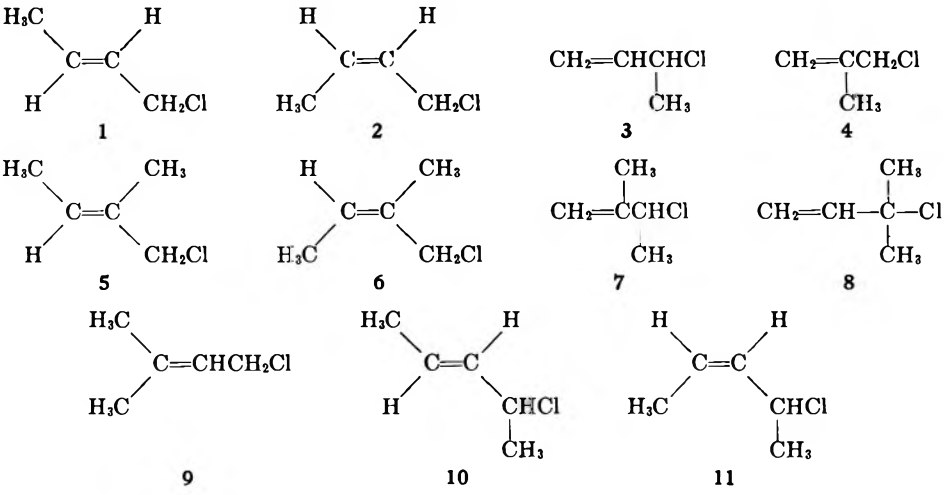
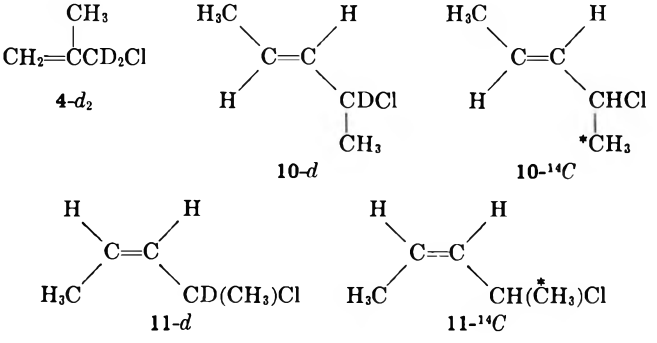
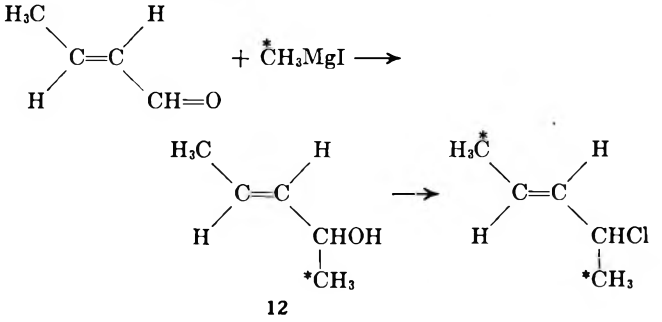


CHART II



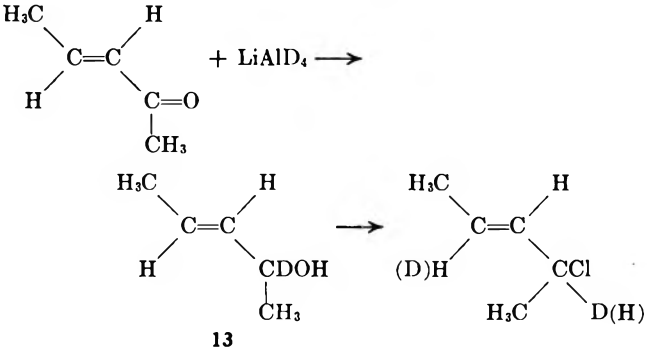
easily prepared by adaptation of established procedures, but enormous difficulties were encountered in the attempted syntheses of ^{2}H- or ^{14}C-labeled **10** and **11**.

A suitable precursor for **10**-^{14}C is alcohol **12** which was prepared by standard methods; degradation of the alcohol confirmed the position of the radioactive carbon. Nearly every attempt to convert **12** into **10**-^{14}C, however, led to complete (or nearly complete)



randomization of the label (see Experimental Section for a compilation of the unsuccessful methods).

The location of the radioactive carbon in **12** and in **10**-^{14}C was determined by ozonolysis[13] and measurement of the activity of the resulting acetaldehyde. Since alcohol **12** was position-specific in its label, we considered the possibility that some or all of the chloride-producing reactions had, in fact, afforded unscrambled **10**-^{14}C and that randomization was occurring during the degradation itself;[15] several reasonably attractive mechanisms for such a process can be imagined. To clarify this point, ^{2}H-labeled alcohol **13** was prepared,



the idea being that one can locate the label in **13** and its derived chloride by nmr analysis both before and after ozonolysis. The numerous failures with radioactive alcohol **12** were once again encountered when **13** was treated with a variety of reagents. Complete or nearly complete scrambling was the general result, the largest label spreads at the α:γ carbons being 57:43 and 65:35 with phosphorous trichloride and phosphorous oxychloride, respectively; in all cases, from 3 to 8% of *cis*-chloride **11** was also produced. It would, therefore, appear that the difficulty resides in the synthesis of the chloride, and, in confirmation of this, ozonolysis of a sample of **10**-*d* having 56% of deuterium at the α carbon and 44% at the γ yielded acetaldehyde which was deuterated to the extent of 44%.

Thus, the method of degradation is reliable, and it must be concluded that none of the alcohol conversions that we tried were very satisfactory. Because of this, the synthesis of the even more labile *cis*-chloride, **11**-*d* or **11**-^{14}C, was not pursued.

The reactions of phenyllithium with monomethyl chloride **3** and dimethyl chlorides **5**, **6**, **7**, **8**, **9**, **10**-*d*, and **10**-^{14}C gave the corresponding coupling product(s) as the only isolable and identifiable materials; in addition to coupling product(s), chlorides **1** and **2** gave small quantities of 1-methyl-2-phenylcyclopropane, and chloride **4** yielded variable amounts of 1-methyl-

(13) This method of degradation was chosen because of its successful application in the analysis of ^{14}C-labeled allyl chloride,[12b,14] and because the conditions can be adjusted to make it milder than other oxidation procedures.

(14) S. H. Sharman, F. F. Caserio, R. F. Nystrom, J. C. Leak, and W. G. Young, *J. Amer. Chem. Soc.*, **80**, 5965 (1958).

(15) This possibility was suggested by Professor W. G. Young, private communication.

TABLE I

YIELDS AND PRODUCT DISTRIBUTIONS IN THE COUPLING OF PHENYLLITHIUM WITH MONO- AND DIMETHYL-SUBSTITUTED ALLYLIC CHLORIDES[a]

	Product yields, %				
	α attack		γ attack		
Allylic chloride[b]	Cis:trans	Total yield	Cis:trans	Total yield	Ratio, α/γ attack
1[c]	0:100	36.3		12.4	74.5/25.5
2[c]	100:0	30.2		9.9	75.3/24.7
3		0.7	17:83	76.2	1.0/99.0
4-d_2		21.7		16.3	57/43
5	0:100[d]	74.8		3.5	95.5/4.5
6	100:0[d]	80.2		6.4	92.6/7.4
7		7.8	30 ± 2:70 ± 2[d,e]	69.8	10.0/90.0
8		Trace		68.2	0/100
9		80.0		Trace	100/0
10-d[f]	g	39.2	g	39.2	50/50
10-d[h]	g	40.0	g	40.0	50/50
10-^{14}C[i]	j	36.6	j	36.6	50/50

[a] The allylic chloride was added to a twofold excess of ethereal phenyllithium at 25°; product yields were determined by quantitative glpc. [b] The isomeric purity of each of the starting materials is given in the Experimental Section. [c] Reference 1a. [d] According to the naming of these compounds as 1-phenyl-2-methyl-2-butenes, the trans compound has the geometry of **5**, and the cis that of **6**. [e] This material was obtained as an inseparable mixture of cis and trans alkenes; the isomer ratio was determined both by nmr peak areas and by glpc (300-ft capillary column, polyphenyl ether). [f] The starting material had 57% deuterium at the α carbon and 43% at the γ and contained 12.5% of the cis isomer. [g] In both cases, the cis:trans alkene ratio was 12:88, but, since neither starting material was free of cis isomer, the mechanistic significance is not clear. [h] The starting material had an α:γ label spread of 65:35 and contained 7% of the cis isomer. [i] The starting material had 58.1% ^{14}C at C_3 and 41.9% at C_1. [j] The cis:trans product ratio was not determined.

cyclopropene.[16,17] The yields and product distributions of the coupling products are summarized in Table I.

With the exception of halides **1**, **2**, and **4**, 70% or more of the starting material was converted into coupling product(s). Competing α elimination with **1**, **2**, and **4** is one reason for the failure to achieve material balance; for the other chlorides, the remainder of material appears to be in the form of unreacted chloride, nondistillable substances (perhaps by elimination of HCl and anionic polymerization of the resulting diene), and high-boiling materials tentatively identified as the coupling products from starting material and biphenyllithium (formed during the preparation of phenyllithium). In no case do we find any C_8 or C_{10} dienes (from Wurtz reaction of the 4- or 5-carbon allylic chlorides), nor are any low-boiling materials (substituted butadienes or dimethylcyclopropenes) produced from the dimethyl compounds.

We can dismiss the possibility that some of the high-boiling materials result from abstraction of the benzylic proton of the hydrocarbon product producing an anion which then couples with starting material.[18] Such a complication would not only lower the overall yield of coupling product but, more seriously, might selectively remove one of the hydrocarbon products from the reaction mixture, thereby making the α/γ attack ratios in Table I unreliable. That this process is not occurring is shown by a number of observations: each of the products from monomethyl compounds **1**–**4** and dimethyl compound **10** can be recovered unchanged when subjected to the reaction conditions; in none of the reaction mixtures are any substituted styrenes found; products having a benzylic deuterium (from chlorides **4**-d_2 and **10**-d) show no loss of the label during the reaction; optically active *cis*- and *trans*-1-phenyl-2-butene-*1-d* containing a full deuterium at the benzylic carbon were obtained from phenyllithium and optically active 3-chloro-*cis*-1-butene-*1-d*.[19] Thus, it is not unreasonable to assume that the lack of material balance is due, exclusively, to processes independent of the coupling reaction. Consequently, the α/γ attack ratios of Table I may be used for meaningful discussion.

Finally it should be noted that coupling products do not result from an alternate path involving halogen–metal exchange between phenyllithium and allylic chloride followed by coupling of the exchange products;[20] in the systems studied, neither chlorobenzene nor any C_8 or C_{10} dienes are among the reaction products. Products also do not arise by protonation of the allylic anion from phenyllithium addition to butadiene or isoprene, since such reactions give only polymeric materials. For control reactions on the lack of isomerization of the starting allylic chlorides during the reaction, see the Experimental Section.

Discussion

Several features are apparent from inspection of the data of Table I.

1. The product distribution from α-methylallyl chloride (**3**) is distinctly different from that of either *trans*- or *cis*-crotyl chloride (**1** and **2**). Similarly, chloride **7** gives a product ratio different from that of either of its allylic isomers **5** or **6**, although the difference is less pronounced. The only other pair of allylic isomers, **8** and **9**, give the same product, free of its isomer.

2. In those cases involving α attack on pairs of geometric isomers (**1** and **2** or **5** and **6**), the stereochem-

(16) 1-Methyl-2-phenylcyclopropane most likely results from phenyllithium addition across the double bond of 3-methylcyclopropene;[1a] α elimination leading to cyclopropene has been conclusively demonstrated to be the first stage in the formation of phenylcyclopropane from allyl chloride and phenyllithium.[12]

(17) Use of halide-free phenyllithium for reaction with chloride **4** provides a highly efficient and convenient synthesis of 1-methylcyclopropene: R. M. Magid, T. C. Clarke, and C. D. Duncan, *J. Org. Chem.*, **36**, 1320 (1971).

(18) Allylbenzene is quantitatively converted by *n*-butyllithium in THF into phenylallyl anion which couples with allyl chloride in high yield: R. M. Magid and S. E. Wilson, unpublished results.

(19) R. M. Magid and E. C. Nieh, *J. Org. Chem.*, **36**, 2105 (1971).

(20) Iodocyclopropanes and methyllithium do couple by such a two-step process: R. M. Magid and S. E. Wilson, *Tetrahedron Lett.*, 4925 (1969).

istry is quantitatively preserved in the product. In cases where γ attack can produce a mixture of geometric isomers, such a mixture does result (**3** and **7**).

3. Introduction of an α-methyl substituent dramatically reduces the α/γ attack ratio (compare allyl chloride[12] with **3**, **4** with **7**, **3** with **8**, **1** with **10**).

4. A γ-methyl group similarly decreases the proportion of reaction at its point of attachment (compare allyl chloride[12] with **1** or **2**, **4** with **5** or **6**, **1** or **2** with **9**, **3** with **10**).

5. A β-methyl substituent tends to increase the α/γ attack ratio, although the effect is less substantial (compare allyl chloride[12] with **4**, **1** with **5**, **2** with **6**, **3** with **7**).

The first of the above features contradicts the observations of Cristol, *et al.*,[3] on the nearly identical product distributions from the reaction of phenyllithium with α-methylallyl chloride (**3**) and crotyl chloride (presumably[1a] a mixture of **1** and **2**). It should be recognized, however, that their separation of products (before the advent of gas chromatography) was accomplished by distillation; consequently, they failed to identify 1-methyl-2-phenylcyclopropane as a product in the crotyl chloride reaction since it most likely codistilled with crotylbenzene.[21] If one adjusts their value of 90–95% crotylbenzene from crotyl chloride by the amount of cyclopropyl compound actually produced, their α/γ attack ratio becomes similar to ours. Thus, one of the criteria for formation of an intermediate may be dismissed. The results with chlorides **5**, **6**, and **7** also do not require a common intermediate nor do our earlier data with labeled allyl chloride.[12] Only chlorides **8** and **9** give the same product distribution (a single compound) and it is possible, although not required, that a change in mechanism to one involving an ionic or radical intermediate has occurred; certainly, the presence of two stabilizing substituents on either the α or γ carbon, could result in such a change. Consistent with this, but once again not demanding it, compound **10** which is substituted at both ends of the allylic system gives equal amounts of α and γ attack.

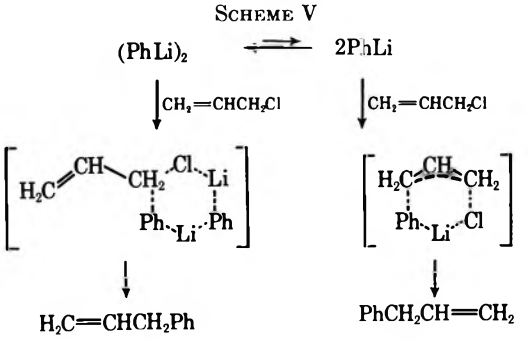
The second feature is in direct conflict with the claim of Wawzonek, *et al.*,[5] that double bond geometry is not preserved in the reactions of phenyllithium with *trans*- and *cis*-crotyl chloride (**1** and **2**). As we have reported earlier,[1a] this apparent loss of stereochemistry is due solely to the use of isomerically impure starting materials. It is significant that even the more highly substituted chlorides **5** and **6** undergo α attack with complete retention of their stereochemical integrity. Thus, another of the criteria for a multistep mechanism must be discarded. One of our principal reasons for investigating the reactions of chlorides **10** and **11** was to ascertain whether substrates bearing substituents that are capable of directly stabilizing an ionic or radical intermediate would still lead to products of retained stereochemistry. Unfortunately, the difficulties in synthesis described earlier prevented our accomplishing this task; the 12% of cis isomer that does result from **10** (Table I, footnote *g*) may merely be due to a combination of γ attack on **10** and α attack on the small amount of cis impurity **11** that is present.

(21) 1-Methyl-2-phenylcyclopropane and *cis*- and *trans*-crotylbenzene are not resolved by a 10-ft, SE-30 glpc column, thus indicating their similar boiling points.

Although all of our data are most simply interpreted without invoking an intermediate, the possibility still exists that ionic or radical[22] species are involved but that they are not so free as to have lost all memory of the structure and stereochemistry of their precursors. One must acknowledge the chance that an intermediate is formed, but that the product-determining transition state is of lower energy than the barriers to significant separation of the leaving group,[2,3] bond rotation,[4] or internal return.[5] The three trends on the influence of α-, β-, and γ-methyl substituents are not especially revealing with regard to drawing mechanistic conclusions, and one can use them in arguing for either concerted or multistep processes.

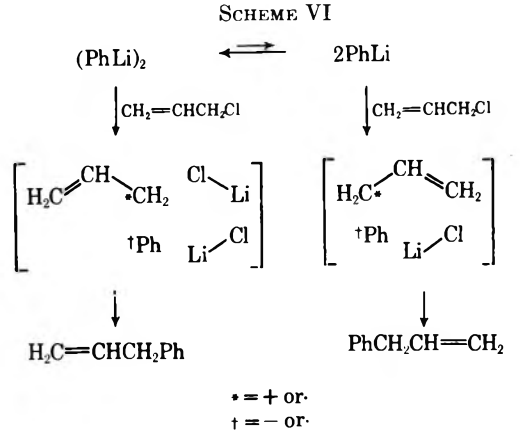
Furthermore, the situation is certainly much more complex than the discussions of other workers would allow. It has been demonstrated that phenyllithium is predominantly dimeric in ether,[23] and the prospect exists that either the monomer or the dimer (or both) is the reactive species in the coupling reaction. One reasonably attractive idea is that α and γ attack are both concerted processes occurring *via* six-membered transition states, the former with dimeric phenyllithium and the latter with monomeric reagent (Scheme V). Kinetic studies should reveal whether the two

SCHEME V



reactions are, indeed, of different kinetic order in phenyllithium, but these have not yet been performed. Should any evidence supporting the idea of an intermediate be found, Scheme V may easily be modified by altering the timing of bondmaking and bondbreaking so that the two transition states are replaced by ionic or radical species (Scheme VI). We prefer to defer

SCHEME VI



(22) Nmr experiments (CIDNP) designed to probe for radical-pair precursors of products gave only negative results: R. M. Magid and F. E. Farrell, unpublished results.

(23) (a) P. West and R. Waack, *J. Amer. Chem. Soc.*, **89**, 4395 (1967); (b) P. West, R. Waack, and J. I. Purmot, *ibid.*, **92**, 840 (1970).

discussion of this point until the following paper in which the stereochemistry of the reaction is described.

Experimental Section

Instruments.—Analytical glpc was performed on a Perkin-Elmer Model 800 gas chromatograph (flame ionization detector) and utilized the following columns: A, 10 ft × 1/8 in., β,β′-oxydipropionitrile (15%) on Chromosorb P; B, a 30 ft × 1/8 in. column composed of a 20-ft section of diethylene glycol succinate (20%) on Chromosorb P (HMDS) and a 10-ft section of Bentone 34 (10%) on Chromosorb P (HMDS); C, 5.5 ft × 1/8 in., Carbowax 20M (20%) on Chromosorb P; D, 20 ft × 1/8 in., Carbowax 20M (10%) on Chromosorb W. In those cases in which quantitative glpc was used for yield determinations, the internal standard method was employed. Peak areas (for yields or product ratios) were measured with a Disc integrator. Preparative glpc was performed on either a Varian Aerograph Model 202-1B gas chromatograph (thermal conductivity detector) or a Hewlett-Packard F & M PrepMaster Jr., Model 776 (flame ionization detector) and utilized the following columns: P, 20 ft × 3/8 in., SE-30 (30%) on Chromosorb P; Q, 10 ft × 3/8 in., SE-30 (20%) on Chromosorb P; R, 8 ft × 1 in., β,β′-oxydipropionitrile (15%) on Chromosorb P; S, 10 ft × 3/8 in., Carbowax 20M (20%) on Chromosorb W; T, 5 ft × 0.25 in., SE-30 (20%) on Chromosorb P; U, 10 ft × 3/8 in., XF-1150 (10%) on Chromosorb P.

Nmr spectra were obtained on a Varian Associates A-56/60A spectrometer. Radioactivity measurements were made with a Packard Tri-Carb Model 3365 liquid scintillation spectrometer. All reactions involving either lithium or organolithium reagents were run in an argon atmosphere.

Materials.—Reagent grade commercial materials were used without further purification, except for the following: thionyl chloride (Matheson Coleman and Bell) was purified by the method of Fieser and Fieser,[24] distilled through a glass helices packed column, and used directly; phosphorus trichloride (J. T. Baker Chemical Co.) was fractionated through a glass helices packed column immediately before use; methyl-^{14}C iodide (50 μCi from Amersham/Searle) was diluted with 500 g of methyl iodide (Matheson Coleman and Bell). Phenyllithium was prepared by the slow addition of bromobenzene in ether to lithium shot[25] in ether at 0–10°, after which the mixture was stored at 0° for 12 hr and filtered through glass wool. By performing this reaction slowly and at relatively low temperature, both the quality and the appearance of the reagent is improved; analysis of the solution was done by the "double titration" method.[26] Halide-free phenyllithium was prepared by the reaction of diphenylmercury and lithium.

Preparation and Purification of Allylic Chlorides.—Each of the starting materials, whether purchased or synthesized, was purified as indicated below and used immediately. The details for 1-chloro-*trans*-2-butene (**1**) and 1-chloro-*cis*-2-butene (**2**) have already been reported.[18a] All of the materials gave spectra consistent with their structures.

A. 3-Chloro-1-butene (3).—Commercial material (Aldrich Chemical Co.) was purified by preparative glpc (column P) and shown to be >99% isomerically pure (column A).

B. 3-Chloro-2-methyl-1-propene-3,3-d_2 (4-d_2).—Commercial methacrylic acid was converted into its acid chloride[27] which was reduced by $LiAlD_4$ according to established procedures;[28] the deuterated alcohol was then converted without allylic rearrangement into chloride 4-d_2 by thionyl chloride and tri-*n*-butylamine in di-*n*-butyl ether.[14] Purification (>99%, column A) was accomplished by preparative glpc (column P); nmr analysis of both the precursor alcohol and chloride 4-d_2 indicated that the samples were >97% dideuterated at the desired position.

C. 1-Chloro-3-methyl-2-butene (9).—Commercially available material (Eastman) was washed with cold 2% $NaHCO_3$, dried over Drierite, and distilled through a glass helices packed column yielding a substance whose nmr spectrum and glpc analysis (column A) indicated >98% purity.

D. 1-Chloro-2-methyl-*trans*-2-butene (5).—Following the procedure of Young, *et al.*,[29] 3-hydroxy-2-methyl-1-butene was treated in dilute ether solution with thionyl chloride at −50°. Glpc analysis (column A) showed that the crude product was composed of 68% of the desired chloride **5**, 30% of *cis*-chloride **6**, and 2% of allylic isomer **7**. Preparative glpc (column R) yielded material which, by nmr and glpc, was judged to be >97.5% isomerically pure; no improvement in purity could be achieved even after a second preparative glpc.

E. 1-Chloro-2-methyl-*cis*-2-butene (6).—Angelic acid (2-methyl-*cis*-2-butenoic acid) was prepared from butanone in five steps, according to the procedure of Buckles and Mock.[30] Reduction with $LiAlH_4$ yielded 1-hydroxy-2-methyl-*cis*-2-butene which, after fractionation through a glass helices packed column, was judged (nmr and glpc analysis, column D) to be >99% pure. Conversion into chloride **6** was achieved by thionyl chloride and tri-*n*-butylamine in ether at −50°.[29] Flash distillation yielded a material which was >90% chloride **6** (column A); preparative glpc (column R) yielded material which was >99% pure.

F. 3-Chloro-2-methyl-1-butene (7).—Chlorine was bubbled into a solution of 2-methyl-2-butene and 1 equiv of $NaHCO_3$ in ether at 0°.[31] Fractional flash distillation yielded a sample which contained 85% (column A) of the desired chloride; two more flash distillations increased the purity to >98%.

G. 3-Chloro-3-methyl-1-butene (8).—The reaction of gaseous HCl with isoprene in ether at −50°,[32] followed by neutralization with $NaHCO_3$ and distillation through a glass helices packed column [bp 30–32° (120 mm)], yielded material which (nmr and glpc analysis, column A) was >97% pure.

H. 4-Chloro-*trans*-2-pentene-4-*d* (10-*d*).—Reduction of *trans*-2-penten-4-one with $LiAlD_4$ produced the corresponding alcohol **13** which, by nmr analysis, was at least 98% monodeuterated at C-4. Reaction of the alcohol with PCl_3 and pyridine at −40°[33] yielded material which, after two flash distillations, was shown (column D) to be composed of 87.5% trans chloride and 12.5% cis; nmr analysis showed that substantial allylic rearrangement had occurred, 57% of deuterium being at C-4 and 43% at C-2. When $POCl_3$ was substituted for PCl_3 in the above reaction, a somewhat greater label spread was achieved: 65% of deuterium at C-4 and 35% at C-2; 7% of the cis chloride was present.

I. 4-Chloro-*trans*-2-pentene-5-^{14}C (10-^{14}C).—The reaction of methyl-^{14}C-magnesium iodide with crotonaldehyde yielded 4-hydroxy-*trans*-2-pentene-5-^{14}C (**12**); the position of the label was confirmed by ozonolysis (>99.5% at C_5). Numerous attempts to convert this alcohol into the corresponding chloride while avoiding allylic rearrangement were made, but most of them failed. To summarize, the following reagents led to complete (or nearly complete) scrambling of the label (as determined by ozonolysis): PCl_3 and pyridine in ether at either 0 or −30°; PCl_3 and LiCl in hexamethylphosphoramide at −5°; hexachloroacetone and triphenylphosphine at 15° (modeled after the established procedure with CCl_4 and triphenylphosphine[34] which is unsuitable because of the similar boiling points of CCl_4 and product); thionyl chloride in ether, with or without pyridine (an attempt to prepare the chloride with complete allylic rearrangement[29]). The procedure of Stork, *et al.*,[35] but with methyllithium replaced by pyridine led to extensive elimination.

The best sample of ^{14}C-labeled chloride was obtained by application of the procedure used to prepare ^{2}H-labeled chloride 10-*d* having a 65/35 label spread. From 4.30 g (0.050 mol) of 4-hydroxy-*trans*-2-pentene-5-^{14}C (**12**) (2.53×10^6 dpm/mol), 7.60 g (0.050 mol) of $POCl_3$, and 1 ml of pyridine was obtained 3.60 g (69%) of labeled chloride, ozonolysis of which produced acetaldehyde whose dimedone derivative had an activity of 1.06×10^6 dpm/mol; thus the distribution of ^{14}C in the chloride is 58.1% at C_5, 41.9% at C_1.

(24) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 1158.

(25) L. R. Worden and A. W. Burgstahler, *J. Chem. Educ.*, **45**, 425 (1968).

(26) H. Gilman and F. K. Cartledge, *J. Organometal. Chem.*, **2**, 447 (1964).

(27) C. E. Rehberg, M. B. Dixon, and C. H. Fisher, *J. Amer. Chem. Soc.*, **67**, 208 (1945).

(28) R. D. Schuetz and F. W. Millard, *J. Org. Chem.*, **24**, 297 (1959).

(29) W. G. Young, F. F. Caserio, Jr., and D. D. Brandon, Jr., *J. Amer. Chem. Soc.*, **82**, 6163 (1960).

(30) R. G. Buckles and G. V. Mock, *J. Org. Chem.*, **24**, 297 (1959).

(31) Adapted from the method of A. Lauchenauer and H. Schinz, *Helv. Chim. Acta*, **34**, 1514 (1951).

(32) A. J. Ultée, *J. Chem. Soc.*, 530 (1948).

(33) (a) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **81**, 703 (1929); (b) H. W. J. Hills, J. Kenyon, and H. Phillips, *J. Chem. Soc.*, 576 (1936).

(34) (a) I. M. Downie, J. B. Lee, and M. F. S. Matough, *Chem. Commun.*, 1350 (1968); (b) R. G. Weiss and E. I. Snyder, *ibid.*, 1358 (1968); (c) R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, **35**, 1627 (1970).

(35) G. Stork, P. A. Grieco, and M. Gregson, *Tetrahedron Lett.*, 1393 (1969).

General Procedure for Ozonolysis of Labeled Allylic Alcohols, Allylic Chlorides, and Coupling Products.—The procedure of Young and coworkers[14] for cleavage of allyl chloride was modified to allow milder conditions and to trap acetaldehyde as it was formed. Excess ozone was bubbled through a solution containing *ca.* 0.02 mol of the substrate in 30 ml of methylene chloride maintained at −15°. Solvent was removed with a rotary evaporator (without external heating) and the residue was added to 5 g of zinc dust and 50 ml of 10% aqueous acetic acid at room temperature. Acetaldehyde, thus generated, was swept by a stream of argon (30 ml/min) through an ice–water condenser and into a dimedone trap (*ca.* 300 ml of 0.1 *N* dimedone in sodium acetate–acetic acid buffer, adjusted to pH 5.8).[36] After *ca.* 30 min, the decomposition was complete; the contents of the trap were acidified to pH 4 with acetic acid. Typically, 80% (based upon dimedone) of the 1:2 derivative, mp 140–143°, was formed. Three recrystallizations from methanol–water followed by drying in a vacuum desiccator provided the pure derivative, mp 142–143°.

General Procedure for Reaction of Allylic Chlorides with Phenyllithium.—All reactions were performed by adding a 20% ethereal solution of 0.02–0.10 mol of freshly purified allylic chloride over 15 min to a twofold excess of 0.7–0.8 *N* phenyllithium in ether at room temperature. The reaction mixture was stirred for 2 hr and was hydrolyzed with water. The organic phase was washed with water, dried over Drierite, and concentrated. Quantitative glpc analysis for product yields (ethylbenzene, internal standard) and product distribution were performed on columns B or C for the monomethyl compounds and A or D for the dimethyl. All materials amounting to more than 1% of the total were purified by reduced pressure distillation followed by preparative glpc using columns M or U for the monomethyl compounds and columns S, T, Q, or U for the dimethyl. All products thus isolated were pure (>99%) and their structures were confirmed by nmr analysis and by comparison with authentic samples when available. For reactions in which low-boiling products (methyl-substituted butadienes and cyclopropenes) were anticipated, a stream of argon was swept through the reaction vessel into a Dry Ice–acetone trap whose contents were analyzed by glpc (column D); in every case, the only materials found were ether and unreacted allylic chloride. High-boiling materials (formed in low yield) which would not distil easily at reduced pressure were analyzed by nmr without further purification; they appeared to be mixtures of polymeric material and the coupling products from biphenyllithium and starting material.

Control Reactions.—All of the products were stable to the reaction conditions. In no case was phenyllithium-promoted isomerization to a substituted styrene detected, and alkenes with a benzylic deuterium showed no loss of label. All of the monomethyl allylic chlorides were subjected to the reaction conditions; analysis of aliquots removed at various times showed no isomerization (positional or geometric) and no conversion into allylic bromide (by reaction with LiBr present in phenyllithium). For the monomethyl allylic chlorides, inverse addition of phenyllithium gave no significant change in product yield or distribution nor did the use of halide-free phenyllithium.

Registry No.—**3**, 563-52-0; **4**, 563-47-3; **5**, 23009-73-6; **6**, 23009-74-7; **7**, 5166-35-8; **8**, 2190-48-9; **9**, 503-60-6; **10**, 18610-33-8; phenyllithium, 591-51-5.

(36) G. W. Gaffney, W. A. Williams, and H. McKennis, Jr., *Anal. Chem.*, **26**, 588 (1954).

The Coupling Reaction of Phenyllithium with Allylic Chlorides. The Stereochemistry of the Reaction[1a]

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The stereochemistry of γ coupling of phenyllithium with optically active 3-chloro-*cis*-1-butene-*1-d* has been determined. The results are interpreted in terms of a mechanism (concerted or stepwise) which proceeds greater than 95% by attack of phenyllithium syn to the leaving group.

In the preceding paper,[2] several mechanisms for the coupling of allylic chlorides with phenyllithium were discussed. Product and geometric isomer data from the reactions of mono- and dimethyl-substituted allylic chlorides led to the conclusion that the coupling at both the α and γ carbons either is a direct one-step process or involves intermediates (ionic or radical) which are separated from products by a relatively low energy barrier (*i.e.*, their lifetimes are not long enough to allow loss of memory of the structure and geometry of their precursors). In this paper, we report on the stereochemistry of the coupling reaction with optically active allylic chlorides.

Results

In order to fully elucidate the stereochemistry of the coupling reaction, a substrate which meets all of the following conditions is required.

1. It must have an asymmetric α-carbon atom. 2. Two different substituents must be present on the γ carbon, and the geometry of the double bond must be well defined. 3. Coupling reaction should occur at both allylic positions, and the α- and γ-coupling products must be cleanly separable, one from the other. 4. γ attack must produce a *separable* mixture of cis and trans olefins. 5. The absolute configuration and maximum rotation of the allylic chloride and of its coupling products should be able to be determined with a reasonable degree of accuracy.

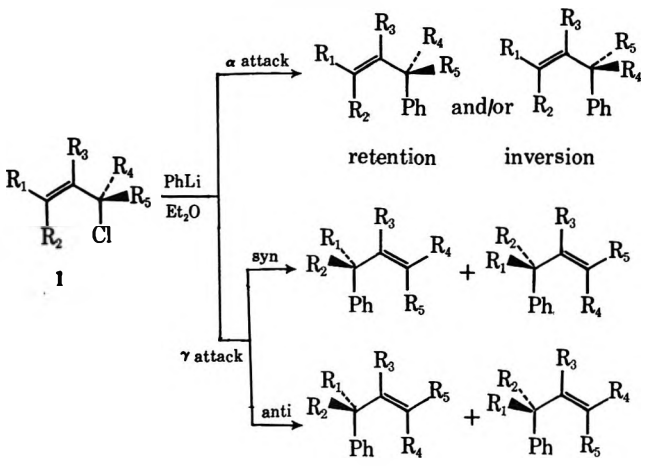
The reaction of phenyllithium with a substrate (of generalized structure **1**) meeting all of these conditions is illustrated in Scheme I.[3] Our initial plan was to use optically active 4-chloro-*trans*-2-pentene (**1**, $R_1 = R_4 = CH_3$; $R_2 = R_3 = R_5 = H$), unsymmetrically labeled with either ^2H or ^{14}C. Unfortunately, we were unable to prepare this material with a sufficiently large label spread and with clearly defined double bond geometry.[2] Furthermore, we were doubtful of the likelihood of obtaining this substance in an optically stable form in view

(1) (a) Partial support of this work by the Robert A. Welch Foundation is gratefully acknowledged, as is the assistance of the National Science Foundation in the purchase of a Varian Associates A-56/60A nmr spectrometer. (b) To whom inquiries should be addressed at the Department of Chemistry, The University of Tennessee, Knoxville, Tenn. 37916.

(2) R. M. Magid, E. C. Nieh, and R. D. Gandour, *J. Org. Chem.*, **36**, 2099 (1971).

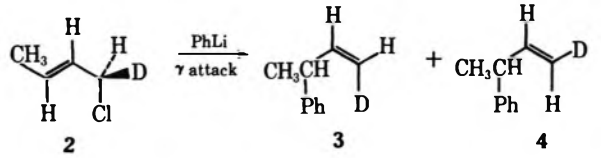
(3) The terms syn or anti used for γ attack refer to processes in which coupling occurs on the same or opposite side of the allylic system, respectively, as the departing chloride.

SCHEME I



of the known tendency of cyclic allylic chlorides to readily racemize *via* ion-pair formation.[4]

We were therefore forced to consider using a less reactive allylic chloride, one that is only monosubstituted. A substrate such as 1-chloro-*trans*-2-butene-*1-d* (**2**), or the corresponding cis isomer, satisfies all but condition 4. The two products of γ attack cannot be separated and, since the newly generated asymmetric centers of **3** and **4** would be of opposite chirality, the total sample would give no rotation.

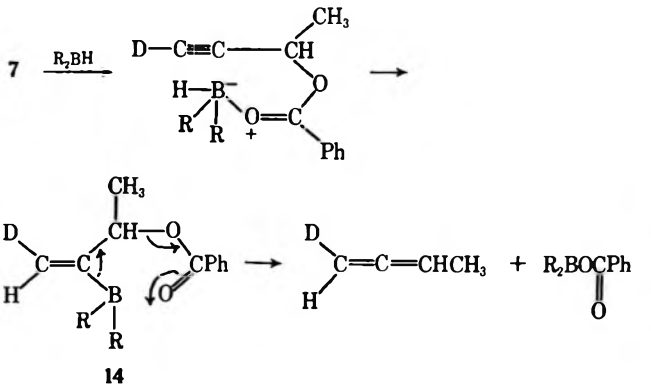


Thus, we turned our attention to optically active 3-chloro-*cis*-1-butene-*1-d* (**13**) as the substrate for this study. Unfortunately, 3-chloro-1-butene is known to couple almost exclusively by γ attack,[2] and thus condition 3 is not met. In order to determine the stereochemistry of α attack, a compound such as **2** is required. Since there are numerous reports on the coupling reactions of organometallic reagents with nonallylic chiral substances,[5] we concentrated our entire effort on the preparation and reactions of **13** for which the stereochemistry of allylic attack can be determined.

The synthesis of optically active 3-chloro-*cis*-1-butene-*1-d* (**13**) is summarized in Chart I. In general, these reactions were performed so as to obtain pure materials at each step; the yields reported in the Experimental Section are for the isolated, >99% pure, products of each reaction. Some of the steps of the synthesis merit a few words of explanation.

Conversion of alcohol **5** into benzoate **6** was necessary for two reasons. First, deuterium exchange on **5** is difficult because its miscibility with water makes isolation of **5** after each exchange laborious; use of **6** and the two-phase exchange system not only avoids this recovery problem but also allows the exchange to be conveniently monitored by nmr. Second, hydroboration of alcohol **5** produces none of the desired reduction product, whereas benzoate **6** gives quite acceptable yields.

The disiamylborane–protonolysis method for stereospecific cis reduction of an alkyne has been studied in some detail,[6] but the reproducibility of yields appears to be rather poor. For example, Brown and Zweifel[6a] claimed an 80% conversion of 1-hexyne into 1-hexene, but the same reaction in the hands of Murray and Williams[6b] gave only 40%. In the case of deuterated benzoate **7**, the literature procedure[6a] gives **8** in only 10–15% yield. We discovered, however, that, if both hydroboration and protonolysis are carried out at −5 to 0° and if protonolysis is performed immediately after completion of the first stage, quite acceptable yields (typically 40%) of **8** could be realized. One can speculate that the low yields with the literature procedure result from a competing reaction in which the initial adduct **14** undergoes intramolecularly catalyzed elimination to an allene before acetic acid is added; **7** proceeds regiospecifically to **14** because of the directing influence of the adjacent ester. A similar rationalization was



offered by Brown and Gallivan[7] in the hydroboration of allylic acetates; Zweifel, *et al.*,[6d] have indeed found that disiamylborane reduction of internal propargylic chlorides yields an intermediate which undergoes intermolecular base-catalyzed elimination to allenes.

That the reduction does, in fact, proceed stereospecifically cis is clearly demonstrated by first-order analysis of the nmr spectra of **8**, **9**, **10**, and **13** as compared to their undeuterated analogs (see Experimental Section for the complete spectral data). Briefly, (1) each of the labeled compounds is lacking the lower field of the two absorptions due to the terminal vinyl hydrogens in unlabeled material;[8] at most, 2% of the trans-reduced product is present. (2) The remaining pair of vinyl hydrogens gives J_{vic} = 10.0 Hz (typical of cis coupling); the other J_{vic} = 16.6–17.3 Hz found in the unlabeled compounds is absent.[9] (3) Each of the deuterated compounds shows coupling of the internal vinyl hydro-

(4) H. L. Goering, T. D. Nevitt, and E. F. Silversmith, *J. Amer. Chem. Soc.*, **77**, 5026 (1955).

(5) (a) J. Sauer and W. Braig, *Tetrahedron Lett.*, 4275 (1969); (b) W. D. Korte and L. Kinner, *ibid.*, 603 (1970); (c) L. H. Sommer and W. D. Korte, *J. Org. Chem.*, **35**, 22 (1970); (d) G. M. Whitesides, W. F. Fischer, Jr., J. S. Filippo, Jr., R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, **91**, 4871 (1969).

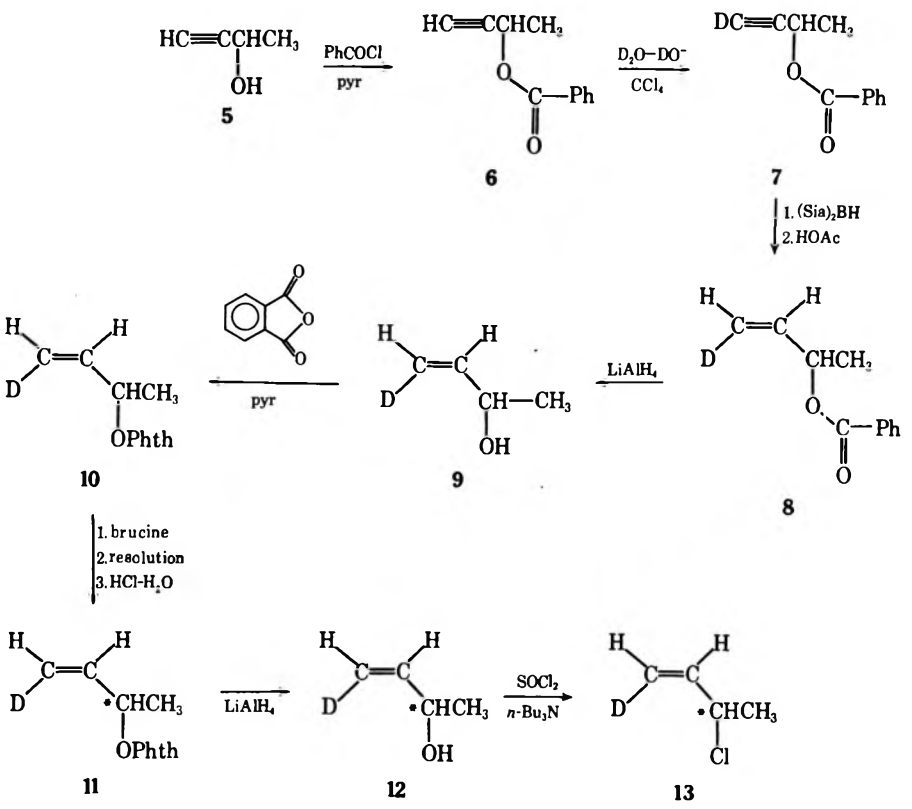
(6) (a) H. C. Brown and G. Zweifel, *ibid.*, **83**, 3833 (1961); (b) R. W. Murray and G. J. Williams, *J. Org. Chem.*, **34**, 1896 (1969); (c) A. Streitwieser, Jr., L. Verbit, and R. Bittman, *ibid.*, **32**, 1530 (1967); (d) G. Zweifel, A. Horng, and J. T. Snow, *J. Amer. Chem. Soc.*, **92**, 1427 (1970).

(7) H. C. Brown and R. M. Gallivan, Jr., *ibid.*, **90**, 2906 (1968).

(8) (a) U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, **25**, 691 (1969); (b) S. W. Tobey, *J. Org. Chem.*, **34**, 1281 (1969).

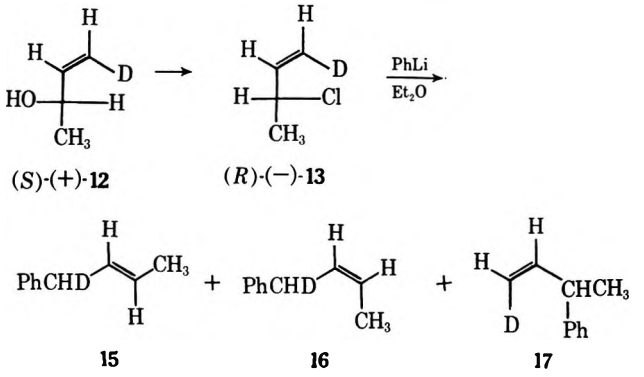
(9) (a) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, p 128 ff; (b) D. J. Pasto and C. R. Johnson, "Organic Structure Determination," Prentice-Hall, Englewood Cliffs, N. J., 1969, p 187 ff.

CHART I



gen to deuterium, J = 2.0–2.5 Hz, as expected for their trans relationship.[9]

Optically active (+)-phthalate **11** (75.6% optically pure[10]) yields (+)-alcohol **12**, known to have the *S* configuration[11a] (75.7% optically pure[11b]), which is converted into (*R*)-(−)-chloride **13** (50.4% optically pure[11]). Reaction of this chloride with phenyllithium produces three coupling products, **15**, **16**, and **17**, in a ratio of 86.0:13.5:0.5. Pure samples of **15** and **16** could be obtained by preparative glpc. Identification was based upon glpc and nmr comparisons with undeuterated materials; both products displayed a full deuterium atom at the benzylic position. The product of α coupling, **17**, could not be isolated but its identity



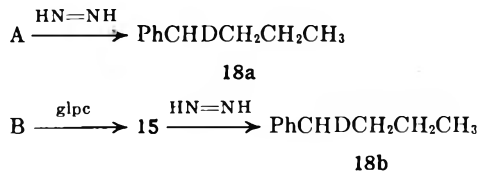
was established by glpc retention times on three different columns. Based upon the preservation of double bond geometry when γ-substituted allylic chlorides are converted into unrearranged coupling products,[2] the stereochemistry shown in **17** is assumed.

(10) J. Kenyon and D. R. Snellgrove, *J. Chem. Soc.*, 1169 (1925).

(11) (a) W. G. Young and F. F. Caserio, Jr., *J. Org. Chem.*, **26**, 245 (1961); (b) K. G. Oliver and W. G. Young, *J. Amer. Chem. Soc.*, **81**, 5811 (1959); (c) W. G. Young and J. S. Franklin, *ibid.*, **88**, 785 (1966).

Careful distillation of the crude reaction mixture afforded an 86.0:13.5:0.5 mixture of **15**, **16**, and **17**, 2.500 g of which was diluted to 9.500 g with a sample of authentic unlabeled racemic materials of exactly the same composition. Spinning band distillation then gave an 86.5:13.5 mixture of **15** and **16**, free of **17** whose removal is important because of its expected large rotation. This sample was diluted with an exactly equal weight of unlabeled racemic **15** and **16** in the same ratio. The mixture now contains 13.2% of deuterated materials.

Since neither the absolute configuration nor maximum rotation of alkenes **15** and **16** is known, this sample was divided into two portions, A and B, which were treated as follows. A was reduced with diimide to (*R*)-(−)-1-phenylbutane-*1-d* (**18a**),[12] α^{27}D −0.0253 ± 0.0002° (neat, l = 0.298). B, by preparative glpc, yielded pure **15** which was similarly reduced to **18b**, α^{27}D −0.0329 ± 0.0002° (neat, l = 0.298). Adjust-

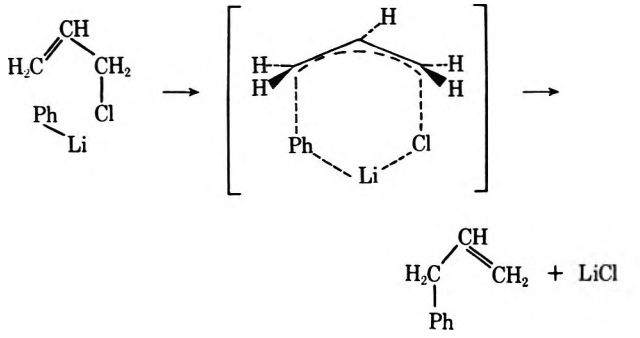


ment of these observed rotations for the fact that the samples are only 13.2% deuterated leads to specific rotations: **18a**, $[\alpha]^{27}$D −0.780° (neat) and **18b**, $[\alpha]^{27}$D −1.02° (neat), corresponding to optical purities[12] of 35.0 and 45.6%, respectively.

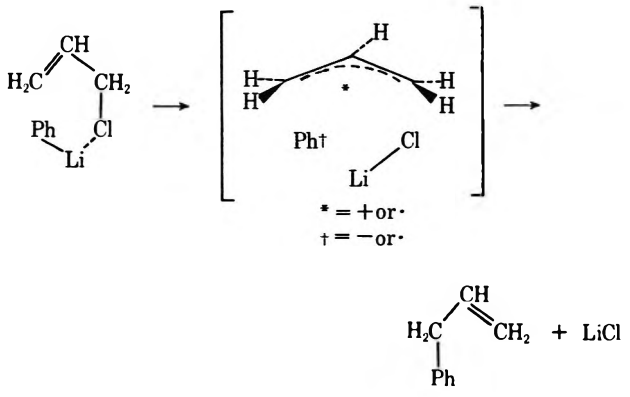
(12) (a) A. Streitwieser, Jr., J. R. Wolfe, Jr., and W. D. Schaeffer, *Tetrahedron*, **6**, 338 (1959); (b) V. E. Althouse, D. M. Feigl, W. A. Sanderson, and H. S. Mosher, *J. Amer. Chem. Soc.*, **88**, 3595 (1966); (c) L. Verbit, *Progr. Phys. Org. Chem.*, **7**, 51 (1970); (d) D. Arigoni and E. L. Eliel, *Top. Stereochem.*, **4**, 127 (1969).

Discussion

One of the plausible mechanisms for γ coupling discussed in the preceding paper[2] involves concerted C–Cl cleavage and C–C formation in a six-membered transition state. Were such a mechanism in fact



operative, the phenyl group would enter syn to the departing halide. Other mechanisms proceeding *via* ionic or radical intermediates could also result in syn attack if it is assumed that coordination of metal with halide is the initial step and that the intermediate collapses to product without rotation about the partial double bond.

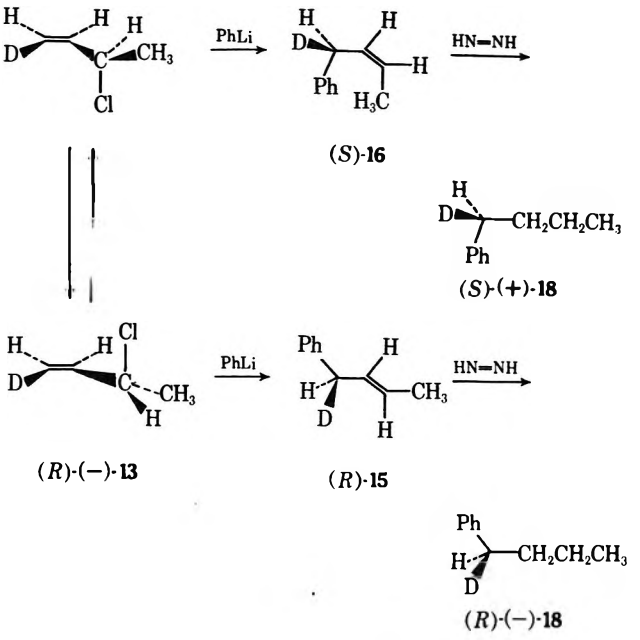


By either view, the mechanism resembles that for the reaction of secondary amines with allylic chlorides[13] for which syn attack has been established with a cyclic allylic ester.[14,15]

Only a relatively long-lived intermediate would fail to produce a highly stereospecific interaction of the reaction partners, and evidence presented earlier[2] would argue against such a situation. A possible variation of the above would involve coordination of phenyllithium to halide concerted with, or followed by, attack of a *second* molecule of phenyllithium either from above (anti) or below (syn) the plane.

The optical rotations observed for reaction of (*R*)-(−)-**13** with phenyllithium can easily be interpreted in terms of a mechanism proceeding by syn attack. Scheme II illustrates the expectations for such a process: cis product **16** should have the *S* configuration and on reduction should produce (*S*)-(+)-**18**,

SCHEME II



whereas trans olefin **15** should be *R* and should give (*R*)-(−)-**18**.

Sample B, above, from which pure trans olefin **15** could be isolated, led to (*R*)-(−)-**18** which was 45.6% optically pure. Since starting chloride (*R*)-(−)-**13** was 50.4% optically pure, this corresponds to an asymmetric transfer to the extent of 91% (*i.e.*, >95% syn attack). Because of the uncertainty in the maximum rotation of **18**,[12] it is not unlikely that syn attack is the exclusive process.

Sample A containing **15** and **16** in a ratio of 86.5:13.5 produced (*R*)-(−)-**18** which was 35.0% optically pure. If one *assumes* 100% syn attack leading to the two components, then the result may be analyzed as follows. Product **18** should be composed of 86.5% of the (*R*)-(−) enantiomer and 13.5% of the (*S*)-(+). Since chloride **13** was only 50.4% optically pure, one expects a contribution of −0.97° from (*R*)-(−)-**18** [(−2.23)·(0.504)(0.865)] and of +0.16° from (*S*)-(+)-**18** [(+2.23)(0.504)(0.135)] making the net rotation −0.81°, in excellent agreement with the observed $[\alpha]^{27}D$ −0.78°. To exactly reproduce this number, one need only assume that both reactions are stereospecific to the extent of 95%.

Thus the conclusions of the preceding paper[2] on the mechanism of coupling are reinforced: either the reaction is concerted or any intermediates go to products without suffering bond rotation.

Experimental Section

Instruments.—Analytical glpc was performed on a Perkin-Elmer Model 800 gas chromatograph (flame ionization detector) and utilized the following columns: A, 5.5 ft × 1/8 in., Carbowax 20M (10%) on Chromosorb W; B, 10 ft × 1/8 in., TCEP (10%) on Chromosorb W; C, 20 ft × 1/8 in., Carbowax 20M (20%) on Chromosorb P; D, 10 ft × 1/8 in., SE-30 (10%) on Chromosorb W. In those cases in which quantitative glpc was used for yield determinations, the internal standard method was employed. Peak areas (for yields or product ratios) were measured with a Disc integrator. Preparative glpc was performed on either a Varian Aerograph Model 202-1B gas chromatograph (thermal conductivity detector) or a Hewlett-Packard F & M PrepMaster Jr., Model 776 (flame ionization detector), and uti-

(13) (a) W. G. Young, I. D. Webb, and H. L. Goering, *J. Amer. Chem. Soc.*, **73**, 1076 (1951); (b) A. Fry, *Pure Appl. Chem.*, **8**, 409 (1964); (c) F. G. Bordwell, *Accounts Chem. Res.*, **3**, 281 (1970).

(14) G. Stork and W. N. White, *J. Amer. Chem. Soc.*, **78**, 4609 (1956).

(15) It is unfortunate that the stereochemistry of reaction with an acyclic substrate has not been determined, since the observed syn attack on the cyclohexenyl system[14] may be due to conformational factors (antiparallel attack) peculiar to such a cyclic system rather than to any inherent stereoelectronic preference of the S_N2' reaction.

lized the following columns: P, 8 ft × 1 in., Carbowax 20M (20%) on Chromosorb W; Q, 10 ft × 3/8 in., TCEP (15%) on Chromosorb W.

Nmr spectra were obtained on a Varian Associates A-56/60A spectrometer. Optical rotations were measured with a Bendix automatic polarimeter; the cell length was 0.298 dm. Rotations were taken either of solutions (reported as $[\alpha]^{T}D$) or of neat liquids (reported as $\alpha^{T}D$ adjusted to a path length of 1 dm or as $[\alpha]^{T}D$ adjusted for path length and density). All reactions involving lithium or organolithium reagents were run in an argon atmosphere.

Materials.—Reagent grade commercial materials were used without further purification except for the following: thionyl chloride (Matheson Coleman and Bell) was purified according to the method of Fieser and Fieser,[16] distilled through a glass helices packed column, and used directly; phenyllithium was prepared as in the preceding paper;[2] diglyme (Matheson Coleman and Bell) was purified according to the procedure of Zweifel and Brown;[17] disiamylborane was prepared according to the literature procedure.[17]

Preparation of Optically Active 3-Chloro-*cis*-1-butene-*1-d* (13).

A. 1-Butyn-3-yl Benzoate (6).—To a mixture of 210 g (3.0 mol) of 1-butyn-3-ol (5), 234 g (3.0 mol) of pyridine, and 300 ml of ether was added 415 g (3.0 mol) of benzoyl chloride over 20 min. The resulting solution was gently refluxed for 2 hr. Pyridine hydrochloride which precipitated upon cooling was removed, and the filtrate was washed with 300 ml of 1 *N* acetic acid, 300 ml of 5% Na_2CO_3, and 300 ml of water, and was dried ($CaSO_4$). Solvent was removed (rotary evaporator) and 1.5 l. of pentane was added. The white prisms which separated were combined with a second crop obtained by concentration of the mother liquor. The combined solids were crystallized once from pentane yielding 432 g (83%) of ester **6**: mp 46–47°; nmr (CCl_4) δ 1.60 (d, 3, J = 7 Hz, methyl), 2.38 (d, 1, J = 2 Hz, acetylenic), 5.54 (d of q, 1, J = 2 and 7 Hz, methine), and *ca.* 7.4 and 8.0 (m, 5, aromatic).

B. 1-Butyn-*1-d*-3-yl Benzoate (7).—Benzoate **6**, 430 g, was dissolved in 500 ml of CCl_4 and was stirred for 6 hr with 20 ml of a 1% solution of sodium methoxide in D_2O (99.8%, Stohler Isotope Chemicals). This procedure was repeated 12 times with fresh portions of D_2O solution until the area of the nmr acetylenic absorption peak had decreased to less than the area of one of the ^{13}C satellites of the methyl protons (*ca.* 98.5% exchanged). The organic layer was dried ($CaSO_4$), concentrated (rotary evaporator), and treated with pentane as above to induce deposition of the product. One crystallization from pentane afforded 414 g (96%) of deuterated ester **7**: mp 46–47°; nmr (CCl_4) δ 1.59 (d, 3, J = 7 Hz, methyl), 5.55 (q, 1, J = 7 Hz, methine), and *ca.* 7.4 and 8.0 (m, 5, aromatic).

C. *cis*-*1*-Buten-*1-d*-3-yl Benzoate (8).—By adaptation of the method of Brown and Zweifel,[6a] a solution of 51.0 g (0.29 mol) of acetylenic benzoate **7** in 100 ml of dried ether was added over 30 min to 400 ml of 0.9 *N* disiamylborane in THF[17] which was stirred under argon and maintained at −5 to 0°. The mixture was stirred at this temperature for an additional 15 min at which time glpc analysis (column A) showed that no starting material was left. With the temperature of the mixture held at −5 to 0°, 200 ml of glacial acetic acid was added over 25 min, and the resulting solution was stirred for an additional 4 hr at the same temperature. The solution was extracted thoroughly with several portions each of ice–water, saturated Na_2CO_3, and water, and was dried ($CaSO_4$). Removal of solvent (rotary evaporator) produced a residue which was distilled through a 14-in. glass helices packed column, and the fraction boiling from 65 to 85° (0.6 mm) was treated with 100 ml of 30% H_2O_2. The organic layer after washing and drying was distilled through a spinning band column giving allylic ester **8** in yields ranging from 30 to 46% (glpc yields, column A, before oxidation were typically 50 to 85%): bp 67–68° (0.5 mm); nmr (CCl_4) δ 1.41 (d, 3, J = 6.8 Hz, methyl), 5.03 (d of d, 1, J = 10.0 and 1.0 Hz, terminal vinyl), 5.52 (m, 1, consisting of a quartet, J = 6.8 Hz, each line of which is split into a doublet of doublets, J = 5.3 and 1.0 Hz, methine), 5.85 (m, 1, consisting of a doublet of doublets, J = 10.0 and 5.3 Hz, each line of which is further split into a 1:1:1 triplet, J = 2.5 Hz, internal vinyl), and *ca.* 7.3 and 7.9 (m, 5, aromatic).

D. 3-Hydroxy-*cis*-1-butene-*1-d* (9).—According to the method of Doering and Zeiss,[18] a solution of 140 g (0.79 mol) of ester **8** in 150 ml of dried ether was added dropwise over 1 hr to a stirred suspension of 25.0 g (0.66 mol) of $LiAlH_4$ in 500 ml of ether at 0–5°. The mixture was allowed to warm to room temperature and was stirred for an additional 1 hr. Saturated NH_4Cl was carefully added and the ether layer was decanted leaving a powdery residue which was thoroughly triturated with several 100-ml portions of ether. The combined ether solutions were washed with saturated NaCl, dried (BaO), and concentrated at atmospheric pressure through a 14-in. glass helices packed column. Distillation of the residue through a spinning band column gave 41.4 g (72%) of allylic alcohol **9**: bp 97–98° (lit.[10] bp 96–97° for 3-hydroxy-1-butene); glpc analysis (column B) >99% pure; nmr (CCl_4) δ 1.19 (d, 3, J = 6.5 Hz, methyl), *ca.* 3.8 (broad s, 1, hydroxyl, concentration-dependent chemical shift), 4.13 (m, 1, consisting of a quartet, J = 6.5 Hz, each line of which is further split into a doublet of doublets, J = 5.5 and 1.0 Hz, methine), 4.88 (d of d, 1, J = 10.0 and 1.0 Hz, terminal vinyl), and 5.75 (m, 1, consisting of a doublet of doublets, J = 10.0 and 5.5 Hz, each line of which is further split into a 1:1:1 triplet, J = 2.5 Hz, internal vinyl).

E. *cis*-1-Buten-*1-d*-3-yl Hydrogen Phthalate (10).—Following the procedure of Kenyon and Snellgrove,[10] a mixture of 41.0 g (0.56 mol) of labeled alcohol **9**, 44.5 g (0.56 mol) of pyridine, and 84.0 g (0.57 mol) of phthalic anhydride in 150 ml of dried ether was stirred at 50° for 5 hr. The cooled clear solution was poured into 500 ml of 2 *N* HCl at 0°. The resulting mixture was stirred vigorously for 5 min, the organic layer was separated, and the aqueous phase was extracted with several 100-ml portions of ether. The combined organic phases were dried ($CaSO_4$) and concentrated (rotary evaporator). Benzene (100 ml) was added and the small amount of phthalic anhydride which precipitated was removed. The solution was again concentrated (rotary evaporator) and the last trace of benzene was removed by heating at 40° (1 mm). The residue, 110 g (89%) of a colorless oil, was the desired phthalate **10**: nmr (CCl_4) δ 1.41 (d, 3, J = 6.3 Hz, methyl), 5.03 (d, 1, J = 10.0 Hz, terminal vinyl), 5.46 (m, 1, consisting of a quartet, J = 6.3 Hz, each line of which is further split into a doublet, J = 6.0 Hz, methine), 5.82 (m, 1, consisting of a doublet of doublets, J = 10.0 and 6.0 Hz, each line of which is further split into a 1:1:1 triplet, J = 2.0 Hz, internal vinyl), *ca.* 7.4 (m, 4, aromatic), and 12.3 (s, 1, carboxyl).

F. Optically Active *cis*-1-Buten-*1-d*-3-yl Hydrogen Phthalate (11).—According to the method of Kenyon and Snellgrove,[10] a solution of 110 g (0.50 mol) of phthalate **10** in 100 ml of acetone was added to 240 g (0.61 mol) of anhydrous brucine in 700 ml of warm acetone. The pale yellow solution was stirred and the white salt which precipitated was crystallized seven times to constant mp 160–162° (lit.[10] mp 120–122°), 43 g. Systematic work-up of the mother liquor yielded two more crops of the less soluble diastereomer, 55 g. Hydrolysis of the combined salts was accomplished by shaking with 400 ml of 4 *N* HCl at 0°. The solution was extracted with ten 50-ml portions of ether, and the combined extracts were dried ($CaSO_4$) and concentrated (rotary evaporator), and the last trace of ether was removed at 40° (1 mm). The residue, 32.5 g (30%), was the desired optically active ester **11**: nmr identical with that of racemic ester **10**; $[\alpha]^{30}D$ +30.6° (c 2.12, EtOH) (75.6% optically pure[10]).

The mother liquors from the fractional crystallization were concentrated and decomposed with 4 *N* HCl, as above, yielding 43.7 g (40%) of optically active ester **11**: $[\alpha]^{30}D$ −19.9° (*c* 5.03, EtOH) (49.2% optically pure[10]).

G. Optically Active 3-Hydroxy-*cis*-1-butene-*1-d* (12).—Optically active (−)-phthalate **11**, 44.0 g (0.20 mol), was treated with 22 g (0.58 mol) of $LiAlH_4$ according to the procedure described above for benzoate **8**. Work-up and spinning band distillation gave 9.8 g (67%) of optically active allylic alcohol **12**: bp 96–98°; $\alpha^{30}D$ −14.1° (neat) (51.1% optically pure[11]). Similarly, 33.2 g (0.15 mol) of (+)-phthalate gave 7.9 g (72%) of (+)-alcohol: $\alpha^{30}D$ +20.9° (neat) (75.7% optically pure[11]).

H. Optically Active 3-Chloro-*cis*-1-butene-*1-d* (13).—Following the procedure of Young, *et al.*,[19] 13.0 g (0.11 mol) of thionyl chloride in 30 ml of dried ether was added dropwise over 30 min to a solution of 7.7 g (0.11 mol) of (+)-alcohol **12** and 21.5 g (0.12 mol) of tri-*n*-butylamine in 180 ml of ether at −50°. The

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(17) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963).

(18) W. von E. Doering and H. Zeiss, *J. Amer. Chem. Soc.*, **72**, 147 (1950).

(19) W. G. Young, F. F. Caserio, Jr., and D. D. Brandon, *ibid.*, **82**, 6163 (1960).

mixture was stirred for 3 hr during which time it slowly warmed to −20° and was flash-distilled into a Dry Ice–acetone trap. The distillate after drying ($CaSO_4$) was shown by glpc (column A) to contain a 69:31 ratio of 3-chloro-1-butene and 1-chloro-2-butene in an overall yield of 92%. Concentration of the solution followed by preparative glpc (column P) gave 4.6 g (48%) of (−)-chloride **13**: $\alpha^{30}D$ −30.8° (neat) (50.4% optically pure[11]); nmr (CCl_4) δ 1.58 (d, 3, J = 6.5 Hz, methyl), 4.42 (m, 1, consisting of a quartet, J = 6.5 Hz, each line of which is further split into a doublet of doublets, J = 7.0 and 0.8 Hz, methine), 5.00 (d of d, 1, J = 10.0 and 0.8 Hz, terminyl vinyl), and 5.86 (m, 1, consisting of a doublet of doublets, J = 10.0 and 7.0 Hz, each line of which is further split into a 1:1:1 triplet, J = 2.5 Hz, internal vinyl).

Reaction of Optically Active 3-Chloro-*cis*-1-butene-*1-d* (13) with Phenyllithium.—Optically active (−)-chloride **13**, 4.0 g (0.044 mol), in ether was added to 0.8 *N* phenyllithium in ether according to the general procedure of the previous paper.[2] Analysis of the crude reaction mixture by glpc (column B) revealed a 73% yield of three hydrocarbons in a ratio of 86.0:13.5:0.5. Preparative glpc (column Q) of a small portion of the crude product led to isolation of the major component, 1-phenyl-*trans*-2-butene-*1-d* (**15**), identified by comparison with unlabeled material and by its nmr spectrum (CCl_4) δ 1.65 (m, 3, methyl), 3.2 (m, 1, methine), 5.4 (m, 2, vinyl), and 7.0 (m, 5, aromatic). A small sample of the next most abundant product was similarly isolated and identified as 1-phenyl-*cis*-2-butene-*1-d* (**16**). The third component was not present in sufficient quantity to permit isolation, but its structure was confirmed as 3-phenyl-1-butene (presumably deuterated at C_1 with cis geometry, **17**) by glpc comparison (columns B, C, and D) with authentic unlabeled material.

Distillation of the crude product yielded 2.80 g of a mixture of **15**, **16**, and **17** in a ratio of 86.0:13.5:0.5, bp 62–64° (10 mm). A 2.500-g portion of this distillate was diluted to 9.500 g with a mixture of optically inactive compounds in exactly the same ratio. Careful distillation through a spinning band column gave 5.15 g of a mixture containing only hydrocarbons **15** and **16** in a ratio of 86.5:13.5 which was then diluted to twice its weight with 5.15 g of the identical mixture of unlabeled materials. This mixture (containing 13.2% of deuterated optically active hydrocarbons) was separated into two portions.

A 5.0-g portion (0.038 mol) was reduced by diimide [formed by treatment of 30.0 g of anhydrous hydrazine in 50 ml of ethanol (containing a few crystals of $CuSO_4$) with oxygen, 30 ml/min for 24 hr].[20] After the usual work-up, the organic layer was distilled through a 6-in. Vigreux column yielding 2.94 g (59%) of 1-phenylbutane-*1-d* (**18a**): bp 62° (10 mm); $[\alpha]^{27}D$ −0.780° (neat).

From a 5.3-g portion, preparative glpc (column Q) gave 4.30 g of pure trans olefin **15** which was reduced with diimide to 2.30 g (53%) of 1-phenylbutane-*1-d* (**18b**): bp 62° (10 mm); $[\alpha]^{27}D$ −1.02° (neat).

Registry No.—**6**, 29333-27-5; **7**, 29333-28-6; **8**, 29333-29-7; **9**, 29333-30-0; **10**, 29333-31-1; (+)-**11**, 29333-32-2; (+)-**12**, 29453-55-2; (−)-**13**, 29333-33-3; (−)-**18**, 29453-61-0; (+)-**18**, 14159-12-7; phenyllithium, 591-51-5.

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Reductions of Some Aliphatic β Diketones with Lithium Aluminum Hydride

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The reduction of β diketones with lithium aluminum hydride ($LiAlH_4$) under forcing conditions affords products of elimination as well as the expected 1,3-diols. The elimination products (unsaturated alcohols) are obtained in yields which correspond to the enol content of the starting diketone. The reaction is highly stereospecific, giving rise to trans olefins exclusively. The unsymmetrical diketone, 2,4-hexanedione, affords two unsaturated alcohols, 3-hexen-2-ol and 2-hexen-4-ol, with the former predominating. The ratio of these two products and their stereochemistry are discussed in light of the most likely reaction mechanism.

The reduction of enolizable β-keto esters,[1,2] malonic enolates,[3] and β diketones[1,4–6] with lithium aluminum hydride ($LiAlH_4$) gives rise to products of elimination as well as the expected 1,3-diols. In discussing the mechanism of the reaction, Dreiding and Hartman[1] proposed that the elimination products (unsaturated alcohols) resulted from the action of $LiAlH_4$ on the enol forms of the compounds, the diols arising from the nonenolized portions. The applicability of Dreiding and Hartman's mechanism to systems other than alicyclic or aromatic β-dicarbonyl compounds has been questioned by other investigators. Marshall, Andersen, and Hochstetler[3] reported that the proposed mechanism could not account for the saturated monoalcohols observed by them in the reduction of malonic enolates and suggested a considerably more complicated reaction scheme. Pohoryles, Sarel, and Ben-Shoshan[5] reacted acetylacetone with lithium aluminum hydride under forcing conditions and observed a higher ratio of elimination product to diol than would be expected from the enol content of acetylacetone. None of these investigators report on the stereochemistry of the unsaturated reaction products.

We have examined the reductions of acetylacetone and 2,4-hexanedione with $LiAlH_4$ in some detail. We were especially interested in identifying all reaction products, in determining the direction of the elimination in the case of the unsymmetrical dione, and in elucidating the stereochemistry of the reaction. This report describes our results and their bearing on the mechanism of the reduction–elimination reaction. Of especial interest is the stereochemical control exhibited during the elimination. The unsaturated reaction products are exclusively trans (Scheme I).

Results

Acetylacetone was a logical choice for most of our studies, because it is the most readily available, sym-

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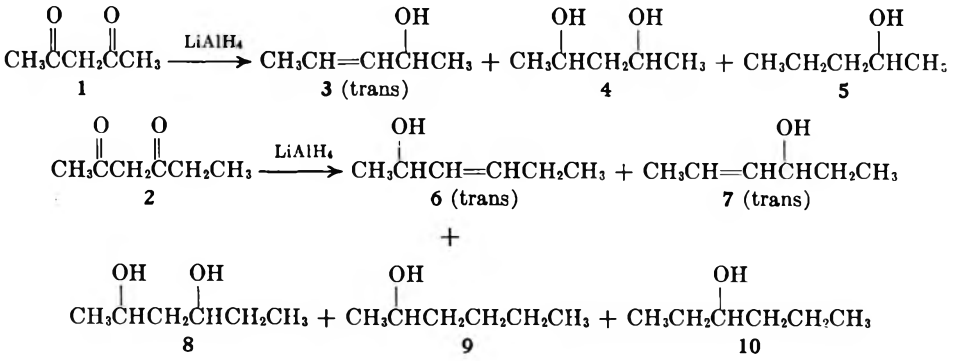
(6) (a) G. Stork and F. H. Clarke, Jr., *J. Amer. Chem. Soc.*, **83**, 3114 (1961); (b) A. Luttringhaus and N. Engelhard, *Angew. Chem.*, **73**, 218 (1961).

Scheme I



metrical 2,4 diketone and because the products of the reduction–elimination reaction are easily separated and identified. The selection of 2,4-hexanedione as a model of an unsymmetrical system was dictated not only by its convenience but also because we were interested in this compound in another connection.

The $LiAlH_4$ reduction of these diones proceeds well only under forcing conditions. A sixfold excess of hydride and 16 hr in refluxing ether were required to complete the reaction.

The results of the $LiAlH_4$ reductions carried out in this study are given in Table I. The data obtained for acetylacetone and 2,4-hexanedione were confirmed in duplicate experiments. The reaction of $LiAlH_4$ with acetylacetone was especially clean. Only three compounds were obtained, *trans* 3-penten-2-ol (**3**), 2,4-pentanediol (**4**), and 2-pentanol (**5**), and these accounted for 96% of the starting material. The reduction of 2,4-hexanedione was more complicated. Two unsaturated and two saturated alcohols are possible as well as the diol[7] and all were observed.

Table I

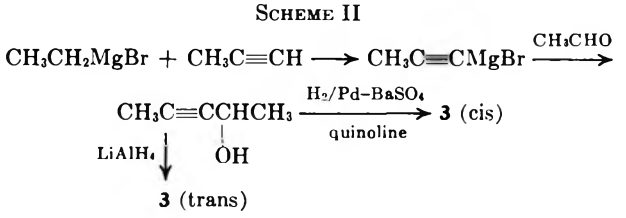
Reduction–Eliminations with $LiAlH_4$[a]

Product	% of product isolated[b]	% yield[b]
Acetylacetone (**1**) (Excess $LiAlH_4$)		
trans-3-Penten-2-ol (**3**)	85.5	82.5
2,4-Pentanediol (**4**)	11.5	11.0
2-Pentanol (**5**)	3.0	3.0
Acetylacetone (**1**) (Stoichiometric $LiAlH_4$)[c]		
trans-3-Penten-2-ol (**3**)	78	
3-Penten-2-one (**12**)	20	
2,4-Pentanediol (**4**)	2	
2-Pentanol (**5**)	Trace	
2,4-Hexanedione (**2**) (Excess $LiAlH_4$)		
trans-3-Hexen-2-ol (**6**)	52.0	41.0
trans-2-Hexen-4-ol (**7**)	21.0	17.0
2,4-Hexanediol (**8**)	18.5	14.5
2-Hexanol (**9**)	6.5	5.0
3-Hexanol (**10**)	2.0	1.5
3-Penten-2-one (Methyl Propenyl Ketone, **12**)		
3-Penten-2-ol[d]	95.5	
2-Pentanol (**5**)	3.5	
1,3-Pentadiene[e]	1.0	
cis-3-Penten-2-ol		
cis-3-Penten-2-ol	100	
trans-3-Penten-2-ol (**3**)	0	
2-Pentanol (**5**)	0	
2,4-Pentanediol (**4**)		
2,4-Pentanediol (**4**)	100	
3-Penten-2-ol (**3**)	0	
2-Pentanol (**5**)	0	

[a] Similar reaction conditions for all reductions. [b] Expressed as mole per cent. [c] Product breakdown was not obtained accurately, since more than 90% of the starting material was recovered. Ratio of 3-penten-2-ol to 3-penten-2-one was 3.5:1. Presence of a trace of 2-pentanol was indicated but not confirmed. No yield data were obtained. [d] Stereochemistry undetermined. [e] Apparently an artifact arising from pyrolysis of the 3-penten-2-ol in the entry port of the gas chromatograph.

The various reaction products were identified by direct comparison of their gas chromatographic behavior and spectral properties with those of authentic samples. The cis and trans isomers of **3** were prepared as shown in Scheme II.

Scheme II



The corresponding isomers of both 3-hexen-2-ol (**6**) and 2-hexen-4-ol (**7**) were synthesized in an analogous fashion. The cis and trans forms of the various unsaturated alcohols are readily separable by gas chromatography.[8] The nmr spectra (see Table II) allowed an unambiguous assignment of the stereochemistry of the double bonds of all of the alcohols. The olefinic protons for the trans configuration are grouped at τ 4.43–4.50 while the olefinic protons for the cis configuration are at τ 4.62. The ir spectra provided confirmatory evidence for our assignments. The structures of all intermediates leading to those olefin alcohols which we synthesized were confirmed by their nmr and ir spectra.

The amount of elimination *vs.* reduction correlates very well with the enol content of the two diones under the reaction conditions (Table III). The per cent of the enol form in ether and $CDCl_3$ was estimated from the nmr spectra by comparing the integrated intensities of the singlets due to the enol (τ 7.97 in $CDCl_3$,

(7) A referee has pointed out that 2,4-hexanediol (**8**) can exist as a mixture of erythro and threo forms. We recognize this possibility but have obtained no evidence that such a mixture actually exist in this instance. We did observe what appeared to be a mixture of diastereomers for 2,4-pentanediol (**4**) in the nmr spectrum and on thin layer plates. Since the character of these mixtures is not important to our discussion, we have chosen to avoid confusion by referring to **4** and **8** in the singular throughout this paper.

(8) The cis forms have somewhat longer retention times. For example, *cis*-3-penten-2-ol has a retention time about 2 min longer than the trans isomer on a 12-ft Carbowax 20M column at 40°. Further details on the chromatography of these materials are given in the Experimental Section.

TABLE II

TABULATION OF NMR SPECTRA

Compd (solvent)	Registry no.	Chemical shift, τ (multiplicity,[a] coupling constant[b]) a	b	c	d	e	f
$CH_3COCH_2COCH_3$ (CDCl$_3$) a b c		7.79 (s)	6.37 (s)	7.79 (s)			
$CH_3COCH{=}COHCH_3$ a b c d	1522-20-9	7.97 (s)	4.42 (s)		7.97 (s)		
$CH_3COCH_2COCH_2CH_3$ (CDCl$_3$) a b c d		7.81 (s)	6.43 (s)	7.48 (q, J_{cd} = 7 Hz)	8.98 (t, J_{cd} = 7 Hz)		
$CH_3COCH{=}COHCH_2CH_3$ a b c d e	29494-98-2	7.99 (s)	4.46 (s)		7.71 (q, J_{de} = 7 Hz)	8.90 (t, J_{de} = 7 Hz)	
$CH_3C{\equiv}CCHOHCH_3$ (CDCl$_3$) a b c d	27301-54-8	8.21 (d, J_{ab} = 2 Hz)	5.53 (qq, J_{ab} = 2 Hz, J_{bd} = 6.5 Hz)	6.06 (s)	8.62 (d, J_{bd} = 6.5 Hz)		
$CH_3C{\equiv}CCHOHCH_2CH_3$ (CDCl$_3$) a b c d e	20739-59-7	8.18 (d, J_{ab} = 2 Hz)	5.75 (tq, J_{bd} = 7 Hz, J_{ab} = 2 Hz)	6.05 (s)	8.32 (dq, J_{bd} = 7 Hz, J_{de} = 7 Hz)	9.03 (t, J_{de} = 7 Hz)	
$CH_3CH_2C{\equiv}CCHOHCH_3$ (CDCl$_3$) a b c d e	109-50-2	8.88 (t, J_{ab} = 7.5 Hz)	7.79 (dq, J_{ab} = 7.5 Hz, J_{bc} = 2 Hz)	5.49 (qt, J_{ce} = 7.5 Hz, J_{bc} = 2 Hz)	5.99 (s)	8.59 (d, J_{ce} = 7.5 Hz)	
trans-$CH_3CH{=}CHCHOHCH_3$ (CCl$_4$) a b b′ c d e		8.36 (dd, J_{ab} = 5 Hz, $J_{ab'}$ = 1 Hz)	4.48 (m)	5.85 (m)	5.64 (s)	8.86 (d, J_{ce} = 6.5 Hz)	
cis-$CH_3CH{=}CHCHOHCH_3$ (CCl$_4$) 24652-50-4 a b b′ c d e		8.38 (d, J_{ab} = 5 Hz)	4.62 (m)	5.44 (dq, $J_{b'c}$ = 6 Hz, J_{ce} = 6 Hz)	5.73 (s)	8.84 (d, J_{ce} = 6 Hz)	
trans-$CH_3CH{=}CHCHOHCH_2CH_3$ (CCl$_4$) a b b′ c d e f		8.34 (dd, J_{ab} = 5 Hz, $J_{ab'}$ = 0.5 Hz)	4.50 (m)	6.13 (dt, $J_{b'c}$ = 6 Hz, J_{ce} = 6 Hz)	5.76 (s)	8.48 (m)	9.14 (t, J_{ef} = 7 Hz)
cis-$CH_3CH{=}CHCHOHCH_2CH_3$ (CCl$_4$) 29478-30-6 a b b′ c d e f		8.37 (d, J_{ab} = 5 Hz)	4.62 (m)	5.73 (dt, $J_{b'c}$ = 6 Hz, J_{ce} = 6 Hz)	5.96 (s)	8.48 (m)	9.14 (t, J_{ef} = 7 Hz)
trans-$CH_3CH_2CH{=}CHCHOHCH_3$ (CCl$_3$) a b c c′ d e f		9.02 (t, J_{ab} = 7 Hz)	7.98 (m)	4.43 (m)	5.78 (m)	6.23 (s)	8.80 (d, J_{df} = 6 Hz)
cis-$CH_3CH_2CH{=}CHCHOHCH_3$ (CCl$_4$) 29478-31-7 a b c c′ d e f		9.04 (t, J_{ab} = 7 Hz)	7.93 (m)	4.63 (m)	5.41 (m)	6.58 (s)	8.82 (d, J_{df} = 6H)
trans-$CH_3CH{=}CHCOCH_3$ (CDCl$_3$) a b c d		8.27 (dd, J_{ab} = 6.5 Hz, J_{ac} = 1.5 Hz)	3.27 (dq, J_{ab} = 6.5 Hz, J_{bc} = 16 Hz)	3.92 (dq, J_{ac} = 1.5 Hz, J_{bc} = 16 Hz)	7.80 (s)		
$CH_3CHOHCH_2COCH_3$ (CDCl$_3$) 4161-60-8 a b c d e		8.83 (d, J_{ab} = 6 Hz)	5.80 (tq, J_{ab} = 6 Hz)	5.80 (s)	7.44 (d, J_{bd} = 6 Hz)	7.85 (s)	
$CH_3CHOHCH_2CHOHCH_3$ (CDCl$_3$)[c] a b c d b c a		8.82 (d, J_{ab} = 6 Hz)	6.04 (tq, J_{ab} = 6 Hz, J_{bd} = 6 Hz)	5.21 (s)	8.49 (t, J_{bd} = 6 Hz)		
$CH_3CH_2CHOHCH_2CHOHCH_3$ (CCl$_4$)[c] a b c d e c d f		9.09 (t, J_{ab} = 6.5 Hz)	8.40 (m)	6.14 (m)	5.16 (s)	8.52 (t, J_{ce} = 6.5 Hz)	8.83 (d, J_{cf} = 6.5 Hz)

[a] s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. [b] The absolute values of the coupling constant are given to ±0.5 Hz. [c] Probably a mixture of diastereomers.

TABLE III

CORRELATION OF ENOL CONTENT AND ELIMINATION *vs.* REDUCTION

Compd	Elimination products, %[a]	Enol contents, %[b] Ether	CDCl$_3$	Lit.
Acetylacetone	88.5	88.5	84.0	81,[c] 91,[d] 94[e]
2,4-Hexanedione	81.5	80[f]	80[f]	

[a] Includes unsaturated alcohols and saturated monoalcohols. [b] Solutions 10% in dione. [c] In cyclohexane: L. W. Reeves, *Can. J. Chem.*, **35**, 1351 (1957). [d] In hexane: J. B. Conant and A. F. Thompson, Jr., *J. Amer. Chem. Soc.*, **54**, 4039 (1932). [e] In ether: K. H. Meyer, *Ber.*, **47**, 826 (1914). [f] Accurate determination is difficult because of multiplicity of peaks and overlapping of signals.

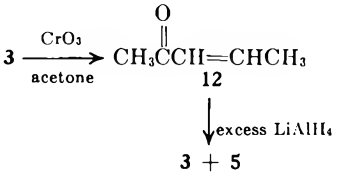
τ 8.05 in ether) and keto (τ 7.79 in $CDCl_3$, τ 7.88 in ether) methyls, the keto methylenes (τ 6.39 in $CDCl_3$, obscured in ether), and the enol –CH= (τ 4.42 in $CDCl_3$, τ 4.55 in ether).

The direction of elimination with the unsymmetrical 2,4-hexanedione (2) was in the favor of the ethyl-substituted olefin, 3-hexen-2-ol (6). This isomer predominated over 2-hexen-4-ol (7) by 2.5:1. This ratio was constant throughout several repetitive experiments.

The stereochemistry of the elimination is especially interesting; the products were trans in all cases. None of the cis olefins were observed, indicating an extraordinary degree of stereochemical control. The trans forms of the olefins are apparently the primary reaction products and do not result from rearrangement of the cis isomers, since *cis*-3-penten-2-ol was recovered unchanged when treated with $LiAlH_4$ under the same conditions employed for reduction of the dione. The corresponding keto alcohols and 1,3-diols were similarly

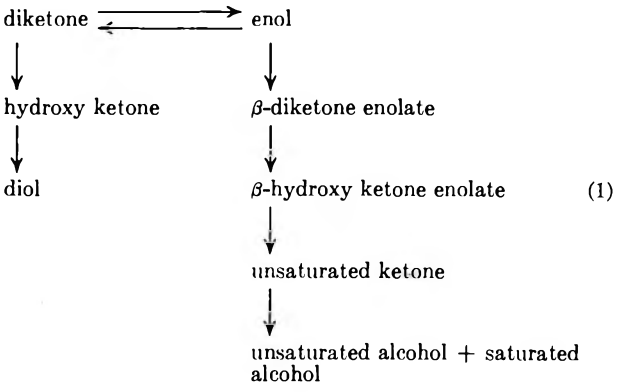
excluded as precursors of the transolefinic alcohols. Reduction of 4-hydroxy-2-pentanone (**11**) with excess $LiAlH_4$ gave a quantitative yield of 2,4-pentanediol (**4**).[9] No unsaturated alcohol was observed. In a separate experiment, **4** was recovered unchanged under the conditions of the reduction–elimination reaction.

Methyl propenyl ketone (3-penten-2-one, **12**), however, could not be excluded as an intermediate to 3-penten-2-ol (**3**). In fact, evidence for its transitory presence during the reaction was obtained. When acetylacetone was treated with a limited quantity of $LiAlH_4$, **12** was obtained along with **3** in the ratio of 1:3.5.[12] In addition, when **12**, prepared by chromic acid oxidation of **3**, was allowed to react with $LiAlH_4$ under the reduction–elimination conditions, both 3-penten-2-ol (**3**) and 2-pentanol (**5**) were isolated. The stereochemistry of the double bond of all of these compounds was found by their nmr spectra (see Table II) to be trans and to remain so during all transformations. The amount of **5** (3%) was virtually the same as that obtained from the reduction–elimination of acetylacetone (Table I). The possibility that **5** might have arisen from **3** must be considered, since reduction of allyl alcohol to 1-propanol has been observed under forcing conditions.[13] However, **3** was recovered unchanged when subjected to the reaction conditions which produced **5** from both **1** and **12**.



Discussion

Our results are consistent with reaction path 1. The two forms of the diketones appear to react independently, the enolic portions giving rise predominantly to the elimination products **3**, **6**, and **7** along with the saturated alcohols **5**, **9**, and **10**, while the diketo forms are reduced normally to the diols. This scheme is supported by the data in Table III and by the fact that we have shown that the intermediates which lead to the diols, *i.e.*, the hydroxy ketones, or the diols themselves are not converted to elimination products



(1)

under the conditions of the reaction. We also demonstrated that compounds resulting from reduction of the enol forms, the unsaturated ketones or unsaturated alcohols, do not give rise to any appreciable quantities of diols.[14]

The saturated alcohols **5**, **9**, and **10** arise from 1,4 addition of hydride to the enones **12**, **16**, and **17** which appear to be true intermediates in the reaction scheme. Several pieces of evidence point strongly in this direction. In the first place, compounds such as **12**, **16**, and **17** with carbonyl functions conjugated to double bonds, frequently afford 1,4 addition products when reduced by $LiAlH_4$ under forcing conditions.[13,15,16] Secondly, a trace of **12** was actually isolated in some of the acetylacetone reductions. Finally, when **12** was reduced under the same conditions as acetylacetone, 2-pentanol (**5**) was obtained in the identical amount, relative to 3-penten-2-ol (**3**), as in the case of the diketone. It appears that elimination of one oxygen occurs before reduction at the second.

Dreiding and Hartman postulated analogous intermediates in the reduction–elimination of alicyclic and aromatic β-dicarbonyl compounds.[1,4] However, their proposed mechanism has been criticized as failing to account for the formation of fully saturated products obtained in the reduction of malonic enolates, and evidence was given for a somewhat more complicated reaction scheme.[3a] In the case of malonic enolates, the reaction may take a somewhat different course.

In the case of the unsymmetrical dione (**2**), the reaction is somewhat more complicated as indicated by Scheme III. Here we have used a convenient cyclic representation for the intermediate enolate **13** although a noncyclic form involving two complexed aluminum atoms would serve as well. The initial hydride can be attached either to a or b, and it is this which ultimately determines the product distribution (*e.g.*, relative amounts of **6** and **9** *vs.* **7** and **10**). The predominant attack occurs at b (adjacent to the ethyl group) which is the more electropositive site. An alternate scheme would involve representing the two possible enols **18** and **19** as existing and reacting separately. The relative amounts of **6** and **7** would then

(9) The 4-hydroxy-2-pentanone (**11**) was prepared in surprisingly good yield (50–60%) by the partial hydrogenation of acetylacetone over platinum black. Previous attempts to hydrogenate acetylacetone to the ketol in which other catalysts were employed have met with varying success. Poor yields were obtained using Raney nickel[10] while rhodium on carbon was more effective.[11] We found no difficulty in stopping at the ketol stage. Only under forcing conditions was some 2,4-pentanediol observed. It appears that good yields of hydroxy ketones such as **11** can be obtained by taking advantage of the high enol content of the diketone. The olefinic function apparently can be reduced preferentially. Our results suggest that platinum black in ethanol is a good choice of catalyst and solvent for this transformation.

(10) P. S. Stutsman and H. Adkins, *J. Amer. Chem. Soc.*, **61**, 3303 (1939).

(11) P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals," Academic Press, New York, N. Y., 1967, pp 265–266.

(12) The unsaturated ketone **12** was identified by gas chromatography (retention time identical with an authentic sample) and time-of-flight mass spectrometry. The intensity ratios of *m/e* 69:41 of near unity and the fact that the intensity of the parent peak (*m/e* 84) is about 30% of the *m/e* 69 peak strongly suggests the trans configuration for **12**; see A. Cornu and R. Massot, "Compilation of Mass Spectral Data," Heyden and Sons Ltd., London, 1966.

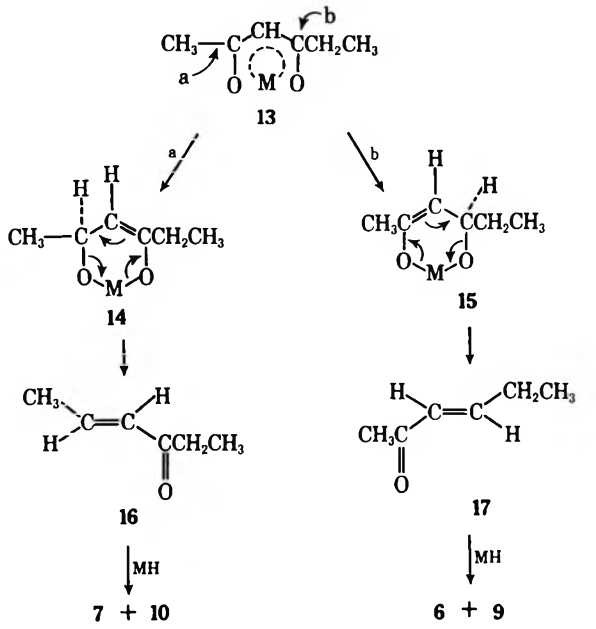
(13) F. A. Hochstein and W. G. Brown, *J. Amer. Chem. Soc.*, **70**, 3483 (1948).

(14) It has been suggested by a reviewer that the enolate of a β-hydroxy ketone, *e.g.*, **14** or **15**, could be reduced to the corresponding diol. We feel this occurs to a very small extent if at all. We have no direct evidence for this but others[2,3a,4] have reported the complete absence of such reductions in the case of pre-formed enolates.

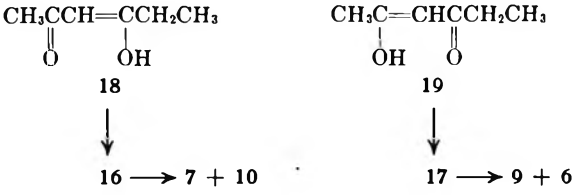
(15) N. B. Gaylord, "Reduction with Complex Metal Hydrides," Interscience, New York, N. Y., 1956, Chapter 15.

(16) J. C. Richer and R. Clarke, *Tetrahedron Lett.*, 935 (1964); M. Mousseron, R. Jacquier, M. Mousseron-Canet, and R. Zagdoun, *Bull. Soc. Chim. Fr.*, **19**, 1042 (1952); W. R. Jackson and A. Zurquiyah, *J. Chem. Soc.*, 5280 (1965).

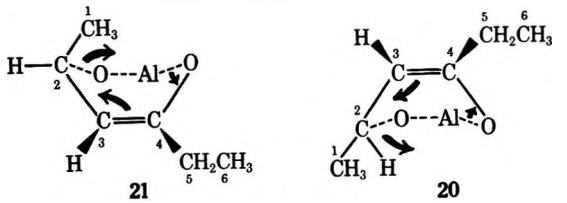
SCHEME III



reflect the proportion of the two enolic forms (an allylic rearrangement occurs during the reaction so that **18** gives rise to **7** and **19** to **6**). Our results do not permit a choice between these two schemes.



One of the most interesting aspects of the reaction is its high degree of stereospecificity. All of the unsaturated alcohols obtained were trans with no trace of the cis isomers observed. As discussed above, the configuration of the double bond in the final products is fixed by the elimination step (**14** → **16** or **15** → **17** in Scheme III). An examination of models as illustrated in structures **20** and **21** shows that there is considerably less crowding when the confirmation around the incipient double bond is trans than if it were cis. The transition state (**21**) for the formation of *cis*-**16** forces



the 1-methyl group into close proximity to the oxygen at carbon 4 with the result of rather severe steric interactions. In the transition state (**20**) for the formation of *trans*-**16**, it is the hydrogen at carbon 2 that interacts with the oxygen at carbon 4, with a resulting reduction of steric crowding. An additional factor is the aluminum–oxygen bonding which we feel would constrain the intermediate **14** or **15** in a cyclic configuration and into a pseudoboat conformation. This would accentuate the interactions described above. It is most probably the formation of the aluminum–oxygen bonds that provides most of the driving force for this elimination reaction.

The synthetic utility of the reduction–elimination reaction has been recognized in only a few instances[6,17] and in these cases the stereochemistry was not important. Because of its stereospecificity, however, the reaction should have considerable value in the preparation of pure trans-unsaturated alcohols. In such syntheses the yield of elimination product can be improved by conditions favoring a high degree of enolization in the parent dicarbonyl compound. This can frequently be accomplished by converting the starting material to its enolate prior to reduction with $LiAlH_4$[2,3,17] or by addition of substances to the reaction which stabilize the enol form of the dicarbonyl compound.[18] It should be emphasized that the effect of such additions on the stereochemical control of the reduction–elimination is not known.[19]

Experimental Section[20]

General.—Commercial acetylacetone (Matheson Co.) and 2,4-hexanedione (Eastman Kodak) were used without purification. Lithium aluminum hydride was obtained from Ventron, Inc., Beverly, Mass. The 2-pentanol, 2-hexanol, and 3-hexanol were obtained from the Matheson Co.; the 2,4-pentanediol from Frinton Laboratories. Authentic samples of *trans*-3-penten-2-ol and *trans*-2-hexen-4-ol were obtained from Aldrich Chemical Co. and J. T. Baker Chemical Co., respectively. The assigned stereochemistry of these samples was confirmed by independent synthesis and by comparison of their infrared traces with published spectra.[21] The reduction–elimination products were identified by comparison of gas chromatographic retention times and, where appropriate, ir and nmr spectra with those of authentic samples.

Reduction–Elimination of Acetylacetone (1) with $LiAlH_4$.—To a slurry of 13.0 g of $LiAlH_4$ in 100 cc of ether was added, dropwise, a solution of 10.0 g (0.1 mol) of acetylacetone in 100 cc of ether. The resulting mixture was refluxed for 16 hr after which the unreacted $LiAlH_4$ was decomposed by the successive addition of 13 ml of water, 10 ml of 20% NaOH, and 20 ml of water. The inorganic salts were filtered and washed with ether. The ether washings were combined and dried over $MgSO_4$, and the solvent was removed. An oily residue (9.4 g) remained. A 1.0-g portion of the residue was removed and analyzed by gas–liquid partition chromatography (glpc). The results are given in Table I. The remaining product was distilled. Two fractions were obtained. The first (6.1 g, bp 115–121.5°) was analyzed by glpc and found to contain 96% *trans*-3-penten-2-ol (**3**) and 4% 2-pentanol (**5**). No other materials were detected. The second fraction (pot residue, 2.0 g) was analyzed by glpc and nmr. The two methods were in excellent agreement and showed that the residue contained 50–52% *trans*-3-penten-2-ol (**3**) and 48–50% of what was probably a mixture of diastereomeric 2,4-pentanediols (**4**). After adjusting for the aliquot removed these two fractions amounted to a 96% recovery of products. A duplicate experiment gave virtually identical results.

(17) J. A. Marshall and N. Cohen, *J. Amer. Chem. Soc.*, **87**, 2773 (1965); J. A. Marshall and N. Cohen, *J. Org. Chem.*, **30**, 2475 (1965); J. A. Marshall and R. D. Carroll, *Tetrahedron Lett.*, 4223 (1965).

(18) For example, L. W. Reeves [*Can. J. Chem.*, **35**, 1351 (1957)] has shown that acetylacetone is converted totally to its enol form in the presence of triethylamine.

(19) Triethylamine, for example, forces enolization by coordinating strongly with the enol hydroxy group of acetylacetone.[18] This may inhibit formation of intermediates such as **15** and thereby reduce the stereospecificity of the reaction. In addition, as discussed above, the mechanism may be different in the case of pre-formed enolates.

(20) The nmr spectra were obtained on a Varian A-60 spectrometer and the infrared spectra on a Perkin-Elmer Model 137 spectrophotometer. Gas chromatographic separations were made on either a F & M 500 (tc detector), F & M 609 (flame ionization), or P & E 226 (capillary) gas chromatograph. A summary of columns used and retention times is given in Table IV.

(21) R. Heilmann, G. de Gaudemaris, and P. Arnaud, *Bull. Soc. Chim. Fr.*, 119 (1957).

Table IV

Gas Chromatography Data

Compd	Retention time (min) on column[a,b] A[c]	B[c]	C[d]	D[d]	E[e]	F[e]	G[e]
cis-3-Hexen-2-ol	21.5[f]			37.5[f]			
trans-3-Hexen-2-ol (6)	21.6[f]	9.8[g]	42.0[h]	33.5[f]	12.2[i]		
cis-4-Hexene-3-ol	22.7[f]						
trans-4-Hexen-3-ol (7)	20.4[f]	9.0[g]	40.0[h]		12.2[i]		4.0[j]
2-Hexanol (9)					9.5[i]		3.0[j]
3-Hexanol (10)					8.0[i]		2.8[j]
2,4-Hexanediol (8)							5.5[j]
cis-3-Penten-2-ol			22.5[h]		7.5[i]		
trans-3-Penten-2-ol (3)			21.0[h]	6.2[i]	7.0[i]	0.8[k]	
2-Pentanol (5)			14.0[h]	4.8[i]	5.0[i]		
2,4-Pentanediol (4)						5.0[k]	
Acetylacetone (1)					2.1[i]		
3-Penten-2-one (12)					6.0[i]		

[a] Column A, 50-ft capillary (0.02 in. i.d.) support coated with Carbowax 1540; B, 50-ft capillary (0.02 in. i.d.) support coated with Carbowax 600; C, 12-ft stainless steel Chromosorb W; D, 10-ft stainless steel (0.25 in. i.d.) packed with 10% Carbowax 20M on Chromosorb W; E, 10-ft stainless steel (0.25 in. i.d.) packed with 10% Carbowax 20M on Chromosorb W; F, 6-ft stainless steel (0.25 in. i.d.) packed with 10% Carbowax 20M on Chromosorb W; G, 4-ft stainless steel (0.25 in. o.d.) packed with 10% Carbowax 20M on Chromosorb W. [b] Du Pont Model 310 curve resolver was used in resolution. [c] Used in P & E Model 226 capillary gas chromatograph, flame ionization detector. [d] Used in F & M Model 609 gas chromatograph, flame ionization detector. [e] Used in F & M Model 500 gas chromatograph, tc detector. [f] At 50°. [g] At 70°. [h] At 40°. [i] At 75°. [j] At 100°. [k] At 125°.

Reduction–Elimination of 2,4-Hexanedione (2) with $LiAlH_4$.—The reduction was carried out with 11.4 g (0.1 mol) of 2,4-hexanedione (2) and 6.5 g of $LiAlH_4$ as described above except that the entire reaction mixture was distilled. (Before distillation the crude mixture was analyzed by glpc. The results are shown in Table I.) Three fractions were collected, weighed, and analyzed by glpc. The first (0.55 g, bp 100–139°) consisted of 60% of a mixture of unsaturated alcohols 6 and 7 and a small amount of 2- and 3-hexanol (9) and (10), 40% of solvent, and a small amount of unreacted 2. Fraction two (6.0 g, bp 139.5–140°) consisted of 90% of the two unsaturated alcohols, 8.5% of 9 and 2.0% of 10, and less than 0.5% of trace impurities. The third fraction was the pot residue; it was analyzed by glpc and nmr and was shown to be 95% 2,4-hexanediol (8) (probably a mixture of erythro and threo forms)[7] and 5% of a mixture of unsaturated and saturated alcohols similar to fraction two. The product recovery amounted to 79%. The two unsaturated alcohols, 6 and 7, were not separable readily by distillation. Each of the above fractions and the crude product mixture were analyzed by glpc using various columns and conditions (see Table IV). In every case the mixture consisted of 71% *trans*-3-hexen-2-ol (6) and 29% *trans*-4-hexen-3-ol (7). None of the corresponding cis isomers were detected.

The reaction was repeated with similar results except that only a 65% recovery of reaction products was obtained.

Reduction of 12 with $LiAlH_4$.—To 2.2 g of $LiAlH_4$ in 25 ml of anhydrous ether was added 2.0 g of 12 in 25 ml of anhydrous ether. The reaction was refluxed overnight and worked up as described above. The product was shown by glpc to contain 95.5% 3, 3.5% 5, and 1% 1,3-pentadiene (see footnote *e*, Table I).

4-Hydroxy-2-pentanone was prepared by reduction of 40 g of 1 in 150 ml of absolute ethanol over a total of 5.5 g of PtO_2. The catalyst was added in five equal portions during the uptake of 1 molar equiv of hydrogen. The product was distilled after removal of the catalyst and solvent. It amounted to a 92% yield, bp 110–112° (90 mm) [lit.[22] bp 74–75° (18 mm)].

Reaction of 2,4-Pentanediol (4) with $LiAlH_4$.—The diol 4, in ether, was refluxed overnight with excess $LiAlH_4$. The reaction was worked up as described above and the crude mixture was analyzed by glpc. Only unchanged starting material was isolated.

Reduction of 4-Ketopentanol-2 (11) with $LiAlH_4$.—To a vigorously stirred suspension of 3.2 g of $LiAlH_4$ in 50 ml of ether was added, dropwise, 2.5 g of 11. The resulting mixture was refluxed overnight and worked up as described. The crude reaction mixture was shown by glpc analysis to contain only 2,4-pentanediol (4).

Reaction of *cis*-3-Penten-2-ol with $LiAlH_4$.—A solution of 1.3 g of *cis*-3-penten-2-ol (contaminated with 15% of the trans isomer) in 10 ml of ether was dropped into a vigorously stirred slurry of 1.8 g of $LiAlH_4$ in 20 ml of ether. The resulting mixture was refluxed overnight and worked up as described above. The solvent was removed by distillation and the residue was analyzed by glpc (Table IV). It contained the identical mixture of *cis*- (85%) and *trans*- (15%) 3-penten-2-ol as the starting material.

Registry No.—1, 123-54-6; 2, 3002-24-2; 3, 3899-34-1; 4, 625-69-4; 5, 6032-29-7; 6, 29478-26-0; 7, 29478-27-1; 8, 19780-90-6; 9, 626-93-7; 10, 623-37-0; 12, 3102-33-8; lithium aluminum hydride, 16853-85-3.

Acknowledgments.—We are indebted to Professor H. C. Brown for several stimulating suggestions concerning the mechanism of the reduction–elimination reaction. We also wish to thank Mr. F. M. Cornman for his technical assistance.

(22) V. I. Esafov, *Zh. Obshch. Khim.*, **33**, 3755 (1963).

Palladium-Catalyzed Reactions of 1,3-Dienes with Active Methylene Compounds. II[1]

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In the presence of palladium and platinum catalysts, 1,3-dienes react with active methylene and methyne compounds such as β-keto esters, β diketones, dialkyl malonates, α-formyl ketones and esters, α-cyano and α-nitro esters, and ethyl phenylsulfonylacetate to form corresponding 2,7-alkadienyl derivatives. In the palladium-catalyzed reactions of active methylene compounds with 1,3-butadiene, 1:2 adducts **1** and 1:4 adducts **2** are obtained as main products, and small amounts of branched 1:2 adduct **3** are isolated as by-products. Addition of isoprene to active methylene compounds gives 2,7-dimethyl-2,7-octadienyl derivatives **4** and **5**, derived from tail-to-tail dimerization of isoprene, almost selectively In contrast to the addition of isoprene, the reaction of 1,3-pentadiene affords a head-to-tail adduct **6**. In the platinum-catalyzed reaction of 1,3-butadiene with active methylene compounds, a ratio of the branched 1:2 adduct **3** to all the adducts is larger than that observed in the palladium-catalyzed reaction, and 1:1 adduct and 1:3 adduct are isolated as by-products besides **1**, **2**, and **3**. A reaction intermediate **7** involving a four-coordinated palladium system derived from the tertiary phosphine complex of palladium(0) is postulated.

Oligomerization of 1,3-butadiene to cyclic or linear products is catalyzed by some transition metal complexes.[2,3] Recently, a new type of linear dimerization of 1,3-butadiene catalyzed by transition metal compounds of group VIII of the periodic table, which is completed by addition of a compound having at least one active hydrogen atom, has been found. Tertiary phosphine complexes of palladium(0) were reported to catalyze the reaction of 1,3-butadiene with methanol and phenol to give 1-methoxy-2,7-octadiene and 1-phenoxy-2,7-octadiene, respectively.[4-6] A mixture of palladium chloride and sodium phenoxide is quite a selective catalyst for the latter reaction.[7] Similar reactions have been reported to take place using primary and secondary amines, carboxylic acids,[5] and active methylene and methyne compounds.[1,8] A reaction of trimethylsilane with 1,3-butadiene catalyzed with (maleic anhydride)bis(triphenylphosphine)palladium(0)[9] and that of amines with the diene in the presence of a triethyl phosphite complex of nickel(0)[10] proceed in a little different way to give corresponding 2,6-octadienyl derivatives.

Part of our work on the reaction of the active methylene and methyne compounds with 1,3-dienes has been reported in a preliminary communication.[1] The present paper describes the reaction in detail.

An active and easily available catalyst is prepared by mixing dichlorobis(triphenylphosphine)palladium and basic sodium compounds such as sodium phenoxide, sodium methoxide, sodium carbonate, and sodium salts of the active methylene and methyne compounds used as the starting reagents. A mixture of palladium chloride and sodium phenoxide showed the same catalytic behavior, but a quite low catalytic activity. Ammonia and pyridine complexes of palladium salts are more effective than palladium chloride but less effective than the triphenylphosphine complex. The low reactivity observed on using palladium chloride and the ammonia and pyridine complexes as catalyst components seems to be due to decomposition of the catalytic species to metallic palladium which appeared during the reaction. On the other hand, in the presence of triphenylphosphine, no separation of metallic palladium was observed and the solution remained pale yellow after completion of the reaction. Zero valent palladium complexes such as tetrakis(triphenylphosphine)palladium(0) and (maleic anhydride)bis(triphenylphosphine)palladium(0) showed catalytic activity without the basic sodium components.

The reaction was applied to compounds with a methylene and methyne group to which two electronegative groups, such as carbonyl, alkoxycarbonyl, formyl, cyano, nitro, and sulfonyl groups, are attached. The reaction of the active methylene compounds with butadiene gave two kinds of main products, 1:2 adducts **1** and 1:4 adducts **2**. At an early stage of the reaction the product consisted mainly of **1**. Further addition of butadiene to **1** afforded **2**.

The reaction products were identified by means of elemental analysis, molecular weight measurement, and ir and nmr spectral measurements.

The results on the reaction of 1,3-butadiene with β-keto esters, β diketones, dialkyl malonates and their derivatives, α-formyl ketones, α-formyl esters, α-cyano and α-nitro esters, cyanoacetamide, and ethyl phenylsulfonylacetate are summarized in Tables I and II. The analytical and physical data of the products are listed in Table III. The infrared spectra of the products showed absorptions due to out-of-plane deformation of $-CH=CH_2$ near 910 and 990 cm^{-1}, and trans $-CH=CH-$ near 960 cm^{-1}. No absorption due to out-of-plane deformation due to cis $-CH=CH-$ was observed. This fact indicates that the internal double bond of the 2,7-octadienyl group consists exclusively or mainly of the trans form.

The reaction of ethyl acetoacetate with 1,3-butadiene in the presence of the $PdCl_2(PPh_3)_2$–PhONa catalyst

(1) G. Hata, K. Takahashi, and A. Miyake, *Chem. Ind. (London)*, 1836 (1969).

(2) G. Wilke, M. Kröner, W. Oberkirch, K. Tanaka, E. Steinrücke, D. Walter, and H. Zimmerman, *Angew. Chem.*, **75**, 10 (1966).

(3) P. Heimbach, P. W. Jolly, and G. Wilke, "Advances in Organometallic Chemistry," Vol. 8, Academic Press, New York, N. Y., 1970, p 29.

(4) S. Takahashi, T. Shibano, and N. Hagiwara, *Tetrahedron Lett.*, 2451 (1967).

(5) S. Takahashi, T. Shibano, and N. Hagiwara, *Bull. Chem. Soc. Jap.*, **41**, 454 (1968).

(6) E. J. Smutny, H. Chung, K. C. Dewhirst, W. Keim, T. M. Shryne, and H. E. Thyret, Preprints of the Symposium on Homogeneous Catalytic Reactions Involving Palladium, 1969, No. B-100.

(7) E. J. Smutny, *J. Amer. Chem. Soc.*, **89**, 6793 (1967).

(8) G. Hata, K. Takahashi, and A. Miyake, French Patent 1,583,249 (1969); S. Hattori, H. Munakata, T. Suzuki, and N. Imaki, Netherland Patent 6,816,008 (1969).

(9) S. Takahashi, T. Shibano, and N. Hagiwara, *Chem. Commun.*, 161 (1969).

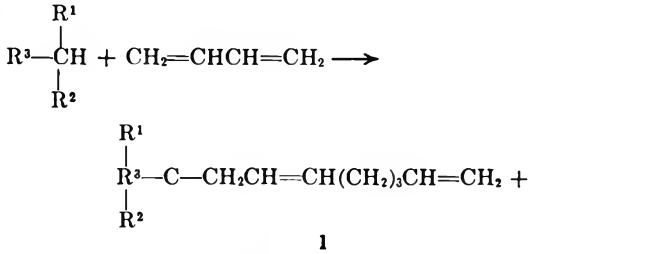
(10) P. Heimbach, *Angew. Chem.*, **80**, 967 (1968).

Table I

Palladium-Catalyzed Reaction of Ethyl Acetoacetate (0.1 mol) with 1,3-Butadiene

Catalyst (mmol)		Butadiene,	Temp,	Time,	Products,[a] %[b]	
Pd compd	Basic Na compd	mol	°C	min	CH_3COCHR-$CO_2C_2H_5$	CH_3COCR_2-$CO_2C_2H_5$
$PdCl_2(Ph_3P)_2$ (0.02)	PhONa (2)	0.3	85	25	78	12
$PdCl_2(Ph_3P)_2$ (0.01)	PhONa (1)	0.3	85	60	78	16
$PdCl_2(Ph_3P)_2$ (0.05)	PhONa (3)	0.5	85	210	26	70
$PdCl_2(Ph_3P)_2$ (0.02)	$NaCH(COCH_3)$-$CO_2C_2H_5$ (2)	0.3	85	25	52	1
$Pd(Ph_3P)_4$ (0.25)		0.3	85	30	20	Trace
$Pd(Ph_3P)_2$·MA[c] (0.02)		0.3	85	75	39	0.6
$PdCl_2(Ph_3P)_2$ (0.05)	PhONa (0.4)	0.3	50	30	11	Trace
$PdCl_2(Ph_3P)_2$ (0.05)	PhONa (0.4)	0.3	60	30	59	3
$PdCl_2(Ph_3P)_2$ (0.05)	PhONa (0.4)	0.3	70	30	63	4
$PdCl_2(Ph_3P)_2$ (0.05)	PhONa (0.4)	0.3	85	30	72	28
$PdCl_2$ (2)	PhONa (6)	0.3	130	180	63	6
$Pd(NO_2)_2(NH_3)_2$ (0.5)	PhONa (5)	0.3	85	120	70	22
$PdCl_2(NH_3)_2$ (0.5)	PhONa (5)	0.3	85	120	82	5
$PdCl_2(Py)_2$ (0.5)	PhONa (5)	0.3	85	120	69	4
$PdCl_2(Ph_3As)_2$ (0.5)	PhONa (5)	0.3	85	120	53	

[a] R = $-CH_2CH{=}CH(CH_2)_3CH{=}CH_2$. [b] Based on ethyl acetoacetate employed. [c] MA = maleic anhydride.



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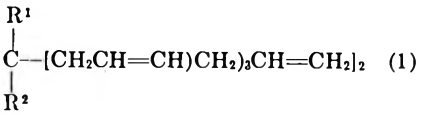
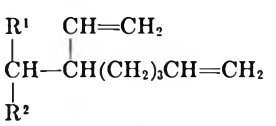


2 (R^3 = H)

1	2	R^1	R^2	R^3
a	a	$COCH_3$	$CO_2C_2H_5$	H
b	b	$COCH_3$	CO_2CH_3	H
c	c	$COCH_3$	$COCH_3$	H
d	d	$CO_2C_2H_5$	$CO_2C_2H_5$	H
e	e	CO_2CH_3	CO_2CH_3	H
f		CHO	$CO_2C_2H_5$	Ph
g		$COCH_3$	CN	CH_3
h	h	COPh	CN	H
i	i	$CO_2C_2H_5$	CN	H
j	j	CN	CN	H
k	k	$CONH_2$	CN	H
l	l	$CO_2C_2H_5$	NO_2	H
m		$CO_2C_2H_5$	SO_2Ph	H

gave **1a** and **2a** as major products. The reaction occurred slowly at 50° but quite rapidly at 85°, as shown in Table I. Acetylacetone and diethyl malonate reacted with the diene to give **1c** and **2c**, and **1d** and **2d**, respectively. Selectivities of the products based on the converted active methylene compounds in the above three reactions were about 90%. As by-products, small amounts of branched 1:2 adducts, *i.e.*, 1-vinyl-5-hexenyl derivatives **3**, were isolated. Ethyl acetoacetate and acetylacetone were more reactive than diethyl malonate. The effectiveness of the catalyst is shown by the fact that 10,000 molecules of ethyl acetoacetate per molecule of dichlorobis(triphenylphosphine)palladium could react in 60 min, as shown in Table I.



3a,c,d

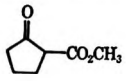
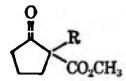
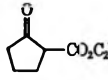
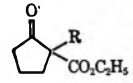
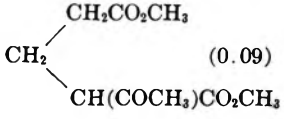
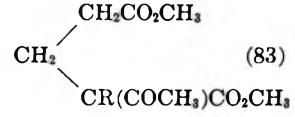
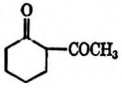
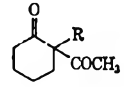
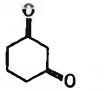
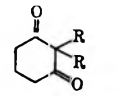
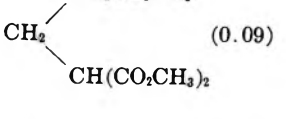
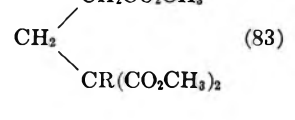
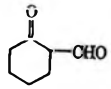
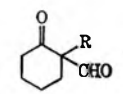
Ethyl 2-oxocyclopentanecarboxylate, 2-acetylcyclohexanone, and trimethyl 1,1,3-propanetricarboxylate reacted with the diene to yield the corresponding 2,7-octadienyl derivatives in 73, 87, and 83% yields, respectively. The reaction of the diene with 2-oxocyclohexanecarbaldehyde, 2-oxocyclododecanecarbaldehyde, and ethyl phenylformylacetate also afforded the 1:2 adducts in high yields. Ethanolysis of 2-acetyl-2-(2,7-octadienyl)cyclohexanone which was obtained from the above reaction resulted in the formation of 2-(2,7-octadienyl)cyclohexanone. The same compound was obtained by elimination of the formyl group of 1-(2,7-octadienyl)-2-oxocyclohexanecarbaldehyde, as expected. Although it seemed certain that the product from the reaction of 1,3-cyclohexanedione with the diene contained a 1:2 adduct besides a 1:4 adduct, the 1:2 adduct has not been identified owing to a poor separation in a fractional distillation.

β-Keto esters, β diketones, α-formyl ketones, and α-formyl esters are in equilibrium between keto and enol forms. Therefore, it might be possible that the hydroxy groups of the enol forms react with 1,3-butadiene to yield 2,7-octadienyl derivatives in which the octadienyl group is bonded to the oxygen atom, as methanol and phenol do. No such products, however, were observed. The addition of 1,3-butadiene to the carbon atom of the active methylene and methyne is quite selective.

Compounds having a cyano group in place of a carbonyl or an ester group of β-keto esters reacted in the same way. The reaction of ethyl cyanoacetate with 1,3-butadiene gave the linear adducts **1i** and **2i** with a small amount of a branched adduct, ethyl (1-vinyl-5-hexenyl)cyanoacetate. The results on the reaction of the diene with 3-oxo-2-methylbutyronitrile, cyanoacetamide, benzoylacetonitrile, and malononitrile are listed in Table II. Low yields of the products in the reaction of the diene with nitroacetone and ethyl nitroacetate seem to be due to decomposition of the catalyst. Ethyl (phenylsulfonyl)acetate reacted with the diene to yield **1m** in a 91% yield.

TABLE II

PALLADIUM-CATALYZED REACTION OF ACTIVE METHYLENE AND METHYNE COMPOUNDS WITH 1,3-BUTADIENE

Active methylene and methyne compd (mol)	BD,[a] mol	Catalyst, mmol: $PdCl_2(Ph_3P)_2$	Catalyst, mmol: Basic Na compd	Temp, °C	Time, min	Products,[b] (%[c])	
β-Keto Esters							
$CH_3COCH_2CO_2CH_3$ (0.1)	0.3	0.02	PhONa (2)	85	25	$CH_3COCHRCO_2CH_3$ (61)	$CH_3COCR_2CO_2CH_3$ (7)
$CH_3COCH_2CO_2CH_3$ (0.25)	0.6	0.07	MeONa (4)	85	140	$CH_3COCHRCO_2CH_3$ (43)	$CH_3COCR_2CO_2CH_3$ (11)
 (0.053)	0.2	0.02	PhONa (1.5)	85	90	 (93)	
 (0.053)	0.2	0.02	PhONa (1.5)	85	90	 (73)	
 (0.09)	0.4	0.05	CH_3ONa (1)	85	180	 (83)	
β Diketones							
$CH_3COCH_2COCH_3$ (0.1)	0.3	0.02	PhONa (2)	85	180	$CH_3COCHRCOCH_3$ (62)	$CH_3COCR_2COCH_3$ (18)
$CH_3COCH_2COCH_3$ (0.1)	0.3	0.02	PhONa (2)	85	25	$CH_3COCHRCOCH_3$ (13)	...
$CH_3COCH_2COCH_3$ (0.15)	0.45	3[d]	$NaCH(COCH_3)_2$ (9)	135	180	$CH_3COCHRCOCH_3$ (7)	...
 (0.2)	0.5	0.02	PhONa (1)	85	130	 (87)	
 (0.036)	0.11	0.2	MeONa (2)	85	60	 (22)	
Malonates							
$CH_2(CO_2C_2H_5)_2$ (0.1)	0.3	0.02	PhONa (2)	85	180	$RCH(CO_2C_2H_5)_2$ (47),	$R_2C(CO_2C_2H_5)_2$ (2)
$CH_2(CO_2CH_3)_2$ (0.1)	0.3	0.2	PhONa (6)	85	180	$RCH(CO_2CH_3)_2$ (49),	$R_2C(CO_2CH_3)_2$ (3)
 (0.09)	0.3	0.5	CH_3ONa (5)	85	105	 (83)	
α-Formyl Ketones and α-Formyl Esters							
 (0.2)	0.5	0.03	PhONa (1)	85	90	 85)	

(0.05)	0.15	0.1	CH_3ONa (2)	85	60	(87)	
$PhCH(CHO)CO_2C_2H_5$ (0.1)	0.3	0.1	CH_3ONa (1)	85	7	$PhCR(CHO)CO_2C_2H_5$ (90)	
α-Cyano Ketones and α-Cyano Esters							
$CH_3COCH(CH_3)CN$ (0.38)[e]	0.12	0.25	PhONa (2.5)	85	900	$CH_3COCR(CH_3)CN$ (66)	
$PhCOCH_2CN$ (0.05)[e]	0.12	0.13	PhONa (1.3)	85	60	$PhCOCHRCN$ (47),	$PhCOCR_2CN$ (35)
$PhCOCH_2CN$ (0.05)[e]	0.25	0.25	PhONa (2.5)	85	900	$PhCOCHRCN$ (trace),	$PhCOCR_2CN$ (80)
$NCCH_2CO_2C_2H_5$ (0.1)	0.3	0.25	PhONa (2.5)	85	60	$NCCHRCO_2C_2H_5$ (23),	$NCCR_2CO_2C_2H_5$ (46)
α-Nitro Ester							
$O_2NCH_2CO_2C_2H_5$ (0.05)[e]	0.15	0.25[f]	PhONa (2.5)	85	1020	$O_2NCHRCO_2C_2H_5$ (61),	$O_2NCR_2CO_2C_2H_5$ (trace)
$O_2NCH_2CO_2C_2H_5$ (0.05)[e]	0.15	0.25	PhONa (2.5)	85	1200	$O_2NCHRCO_2C_2H_5$ (43),	$O_2NCR_2CO_2C_2H_5$ (18)
Miscellaneous							
$NCCH_2CN$ (0.1)[e]	0.3	0.25[f]	PhONa (2.5)	85	60	NCCHRCN (10),	$NCCR_2CN$ (34)
$NCCH_2CONH_2$ (0.05)[g]	0.25	0.25	PhONa (2.5)	85	900	$NCCHRCONH_2$ (trace),	$NCCR_2CONH_2$ (67)
$PhSO_2CH_2CO_2C_2H_5$ (0.05)	0.15	0.25	PhONa (2.5)	85	1440	$PhSO_2CHRCO_2C_2H_5$ (91)	

[a] BD = 1,3-butadiene. [b] R = $-CH_2CH{=}CH(CH_2)_2CH{=}CH_2$. [c] Based on the active methylene and methyne compounds employed. [d] $PdCl_2$. [e] 15 ml of benzene as a solvent. [f] $Pd(Ph_3P)_4$. [g] A mixture of 10 ml of benzene and 30 ml of THF as solvent.

Addition of isoprene to ethyl acetoacetate resulted in the formation of 2,7-dimethyl-2,7-octadienyl derivatives **4a** and **5a** in 95% yield (eq 2, Table IV, p 2121).

According to positions of the methyl groups on the chain, there are four possible dimethyl-2,7-octadienyl chains if the dimerization of isoprene occurs at random. However, the reaction has been found to afford the isomers derived from tail-to-tail dimerization of isoprene almost selectively. In the palladium-catalyzed reaction of phenol with isoprene, the lower selectivity (55%) of the product due to the tail-to-tail dimerization of isoprene has been reported.[6] The compounds **4a** and **5a** showed an ir absorption at 886 cm^{-1} due to out-of-plane deformation of $>C{=}CH_2$ and an nmr signal due to the olefinic protons at τ 5.4 (s, 2 H), which apparently indicate that one of the methyl groups of the side chain is on C-7. A doublet at τ 7.6 ascribed to the C-1 protons of the side chain of **4a** and a singlet at τ 7.4 due to those of **5a** show that the other methyl group is attached to C-2 but not to C-3. Acetylacetone also reacted with isoprene to afford **4c** and **5c** in 91% yield. The nmr spectrum of **4c** showed two kinds of signals due to the C-1 protons of the side chain. A doublet at τ 7.5 and a singlet at τ 7.1 are ascribed to the keto and enol form of **4c**, respectively. The ratio of the keto form to the enol one was 6:4.

Addition of 1,3-pentadiene to ethyl acetoacetate yielded a 2:1 adduct. Absorptions due to out-of-plane deformation of $-CH{=}CH_2$ at 912 and 994 cm^{-1} and to *trans*-CH=CH– at 973 cm^{-1} and a doublet due to an active methyne proton at τ 6.8 indicate that the product has the structure **6**. In contrast to the tail-to-tail addition of isoprene, this reaction affords the product derived from a head-to-tail addition of the 1,3-diene.

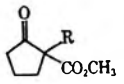
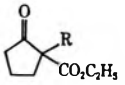
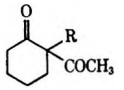
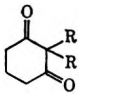
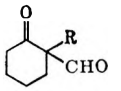
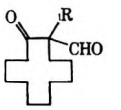
6

The reaction of 2,3-dimethyl-1,3-butadiene with ethyl acetoacetate resulted in the formation of ethyl 2-acetyl-2,3,6,7-tetramethyl-2,7-decadienoate. The reactivity of the diene was very low compared with the reactivities of 1,3-butadiene and isoprene.

As platinum complexes often show the same catalytic behavior as palladium complexes, it is expected that platinum complexes would also catalyze the reaction of the active methylene compounds with 1,3-butadiene. In fact, the same adducts as obtained in the palladium-catalyzed reactions were formed. A combination of $PtCl_2(Ph_3P)_2$ and sodium phenoxide catalyzed the reaction of acetylacetone with 1,3-butadiene to afford the same products as formed in the palladium-catalyzed reaction. The ratio of the branched 1:2 adduct **3c** to all the adducts was 0.16. The value is larger than that observed in the palladium-catalyzed reaction (0.04). It is interesting to note that the reaction catalyzed by a combination of $Pt(Ph_3P)_4$ and sodium phenoxide gave 1:1 and 1:3 adducts as well as the 1:2 and 1:4 adducts (eq 3). Apparently the platinum catalysts were much less effective than the palladium catalysts.

TABLE III

PHYSICAL AND ANALYTICAL DATA OF THE PRODUCTS[a]

Product[b]	Registry no.	Bp, °C (mm)	$n^{25}D$	Empirical formula	Molecular weight Calcd	Found
$RCH(COCH_3)_2$	29330-76-5	135–6 (7)	1.4800	$C_{13}H_{20}O_2$	208	208[c]
$R_2C(COCH_3)_2$	29330-77-6	170–1 (3)	1.4837	$C_{21}H_{32}O_2$	316	316
$CH_2{=}CH(CH_2)_3CH{=}CHCH_2C(CH_2CH{=}CHCH_3)(COCH_3)_2$	29331-16-6	129–30 (3)	1.4800[d]	$C_{17}H_{26}O_2$	264	257
$CH_2{=}CH(CH_2)_3CH(CH{=}CH_2)CH(COCH_3)_2$	26450-24-8	105–7 (11)	1.4630	$C_{13}H_{20}O_2$		
$CH_2{=}CHCH(CH_3)CH(COCH_3)_2$	29149-83-5	199	1.4497	$C_9H_{14}O_2$	154	155
$RCH(COCH_3)CO_2C_2H_5$	26561-31-9	139 (5)	1.4580	$C_{14}H_{22}O_3$	238	238[c]
$R_2C(COCH_3)CO_2C_2H_5$	26561-32-0	189 (5)	1.4758	$C_{22}H_{34}O_3$	346	346[c]
$CH_2{=}CH(CH_2)_3CH(CH{=}CH_2)CH(COCH_3)CO_2C_2H_5$	29085-37-8	98–102 (20)	1.4539	$C_{14}H_{22}O_3$	238	232
$RCH(COCH_3)CO_2CH_3$	29330-83-4	111 (1.5)	1.4588	$C_{13}H_{20}O_3$	224	228
$R_2C(COCH_3)CO_2CH_3$	29330-84-5	181 (3.5)	1.4775	$C_{21}H_{32}O_3$	332	335
$RCH(CO_2CH_3)_2$	29330-85-6	111–7 (1)	1.4563	$C_{13}H_{20}O_4$	240	238
$R_2C(CO_2CH_3)_2$	29330-86-7	162 (1)	1.4735	$C_{21}H_{32}O_4$	348	351
$RCH(CO_2C_2H_5)_2$	29330-87-8	134–5 (3)	1.4496	$C_{15}H_{24}O_4$	268	276
$R_2C(CO_2C_2H_5)_2$	29330-88-9	179 (2)	1.4672	$C_{23}H_{36}O_4$	376	376[c]
$CH_2{=}CH(CH_2)_3CH(CH{=}CH_2)CH(CO_2C_2H_5)_2$	29330-89-0	100 (1.5)	1.4483	$C_{15}H_{24}O_4$	268	263
	29453-58-5	130 (2)	1.4776	$C_{15}H_{22}O_3$	250	256
	29330-90-3	137–8 (3)	1.4739	$C_{16}H_{24}O_3$	264	260
	29330-91-4	149 (3.5)	1.4759	$C_{16}H_{24}O_2$	248	246
	29330-92-5	149–151 (0.001)	1.4983	$C_{22}H_{32}O_2$	328	325
$CH_3O_2CCH_2CH_2CR(COCH_3)CO_2CH_3$	29453-59-6	154–7 (1)	1.4655	$C_{17}H_{26}O_5$	310	311
$CH_3O_2CCH_2CH_2CR(CO_2CH_3)_2$	29330-93-6	161–2 (1)	1.4652	$C_{17}H_{26}O_6$	326	323
	29330-94-7	158 (4.5)	1.4880	$C_{15}H_{22}O_2$	234	234
	29330-95-8	169–173 (0.02)	1.4993	$C_{21}H_{34}O_2$	318	311
$PhCR(CHO)CO_2C_2H_5$	29330-96-9	156–9 (0.1)	1.5075	$C_{19}H_{24}O_3$	300	306
$RCH(CN)_2$	29330-97-0	115 (2)	1.4626	$C_{11}H_{14}N_2$	174	170
$R_2C(CN)_2$	29330-98-1	174–6 (4)	1.4800	$C_{19}H_{26}N_2$	282	278
$RCH(CN)COOC_2H_5$	29453-60-9	120–120.5 (2)	1.4553	$C_{13}H_{19}NO_2$	221	221
$R_2C(CN)COOC_2H_5$	29330-99-2	161–2 (2)	1.4747	$C_{21}H_{31}NO_2$	329	317
$CH_3CR(CN)COCH_3$	29331-00-8	111–2 (4)	1.4652	$C_{13}H_{19}NO$	205	199
$R_2C(CN)CONH_2$	29331-01-9	172 (0.002)		$C_{19}H_{28}N_2O$	300	294
$RCH(CN)COPh$	29331-02-0	134–6 (10^{-4})	1.5293	$C_{17}H_{19}NO$	253	261
$R_2C(CN)COPh$	29331-03-1	156–8 (10^{-4})	1.5210	$C_{25}H_{31}NO$	361	353
$RCH(NO_2)COOC_2H_5$	29331-04-2	110–2 (2)	1.4619	$C_{12}H_{19}NO_4$	241	239
$R_2C(NO_2)COOC_2H_5$	29331-05-3	154–6 (2)	1.4820	$C_{20}H_{31}NO_4$	349	330
$RCH(SO_2Ph)COOC_2H_5$	29331-06-4	156–7 (10^{-4})	1.5176	$C_{18}H_{24}SO_4$	336	334

[a] All compounds in Tables III and V gave C, H (and N when present) analyses within ±0.4. The analytical data were made available to the editors and to the referees. [b] R = $-CH_2CH{=}CH(CH_2)_3CH{=}CH_2$. [c] Determined by mass spectroscopy. The others were measured by vapor pressure osmometry. [d] $n^{20}D$.

$$\underset{\text{4}}{\overset{R^1}{\underset{R^2}{CH_2=C-CH=CH_2}}} + \underset{\text{5}}{\overset{CH_3}{\underset{R^2}{CH_2=C-CH=CH(CH_2)_3C=CH_2}}} \longrightarrow \underset{\text{6}}{\overset{R^1}{\underset{R^2}{CH_2=C-CH=CHCH_2}}}\overset{CH_3}{\underset{R^2}{C[CH_2C=CH(CH_2)_3C=CH_2]_2}} \quad (2)$$

a, $R^1 = COCH_3$; $R^2 = CO_2C_2H_5$
c, $R^1 = R^2 = COCH_3$

Table IV
Reaction of Active Methylene Compounds with Substituted 1,3-Dienes[a]

Active methylene compd (mol)	1,3-Diene (mol)	Catalyst, mmol: $PdCl_2(PhaP)_2$	Catalyst, mmol: PhONa	Products	Yield, %
$CH_3COCH_2CO_2C_2H_5$ (0.1)	Isoprene (0.3)	0.1	2	$CH_2=C(CH_3)(CH_2)_3CH=C(CH_3)CH_2CH(COCH_3)CO_2C_2H_5$	67
				$[CH_2=C(CH_3)(CH_2)_3CH=C(CH_3)CH_2]_2C(COCH_3)CO_2C_2H_5$	28
$CH_3COCH_2CO_2C_2H_5$ (0.1)	Isoprene (0.3)	0.02	1	$CH_2=C(CH_3)(CH_2)_3CH=C(CH_3)CH_2CH(COCH_3)CO_2C_2H_5$	72
				$[CH_2=C(CH_3)(CH_2)_3CH=C(CH_3)CH_2]_2C(COCH_3)CO_2C_2H_5$	14
$CH_3COCH_2COCH_3$[b] (0.1)	Isoprene (0.33)	0.25	2.5	$CH_2=C(CH_3)(CH_2)_3CH=C(CH_3)CH_2CH(COCH_3)_2$	67
				$[CH_2=C(CH_3)(CH_2)_3CH=C(CH_3)CH_2]_2C(COCH_3)_2$	24
$CH_3COCH_2CO_2C_2H_5$[b] (0.1)	1,3-Pentadiene (0.33)	0.25	2.5	$CH_2=CHCH_2CH(CH_3)CH_2CH=CHCH(CH_3)CH(COCH_3)CO_2C_2H_5$	32
$CH_3COCH_2CO_2C_2H_5$ (0.05)	2,3-Dimethyl-1,3-butadiene (0.15)	0.25	2.5	$CH_2=C(CH_3)CH(CH_3)CH_2CH_2C(CH_3)=C(CH_3)CH_2CH(COCH_3)CO_2C_2H_5$	7

[a] All reactions were carried out at 85° for 20 hr. [b] Benzene (15 ml) was used as a solvent.

$$CH_3COCH_2COCH_3 + CH_2=CHCH=CH_2 \longrightarrow CH_2=CHCH(CH_3)CH(COCH_3)_2 + \mathbf{1c} + \mathbf{3c} + \underset{13\%}{} \quad \underset{21\%}{} \quad \underset{24\%}{}$$
$$CH_2=CH(CH_2)_3CH=CHCH_2\diagdown C(COCH_3)_2 + \mathbf{2c} \quad (3)$$
$$\underset{11\%}{} \qquad CH_3CH=CHCH_2\diagup$$
$$\underset{10\%}{}$$

From the fact that the tertiary phosphine complexes of palladium(0) show catalytic activity, the catalytic species must be derived from the complexes of palladium(0). The following tentative reaction intermediate involving a four-coordinated palladium system may be postulated. The coupling between the substituted allyl group and the other ligand would give

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the product and regenerate a tertiary phosphine complex of palladium(0). A ligand–ligand coupling in acetylacetonato(π-allyl)palladium(II) in the presence of a donor such as carbon monoxide has been reported to take place between the active methylene carbon of the acetylacetone group and the π-allyl group, accompanied by a precipitation of metallic palladium.[11] In our reaction, the addition of the 2,7-octadienyl group to acetylacetone also occurs at the active methylene carbon. The chelation of the active methylene or methyne compounds to palladium atom, however, is not requisite for the reaction, since 1,3-cyclohexanedione, dialkyl malonates, and malononitrile, which are not chelating agents, react smoothly. This fact implies that the active methylene or methyne compounds act as unidentate ligands rather than bidentate ligands. In the former ligand–ligand coupling, there remains a possibility that a conversion of the O-bonded acetylacetone complex to a C-bonded one takes place before the coupling. Several complexes of platinum having C-bonded acetylacetone group(s) such as $Me_3Pt(acac)dpy$,[12] $K[Pt(acac)_2Cl]$,[13] $Na_2[Pt(acac)_2Br_2]\cdot 2H_2O$,[14] and $KPt(acac)_3$[14] have been reported. In the present reaction, such a metal–carbon bonding seems probable.

Experimental Section

Reagents.—$PdCl_2(Ph_3P)_2$,[15] $Pd(Ph_3P)_4$,[16] $Pd(Ph_3P)_2$(maleic anhydride),[17] $Pd(NO_2)_2(NH_3)_2$,[18] $PdCl_2(NH_3)_2$,[19] $PdCl_2(Py)_2$,[20]

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TABLE V

PHYSICAL AND ANALYTICAL DATA OF THE PRODUCTS[a]

Product	Registry no.	Bp, °C (mm)	$n^{25}D$	Molecular weight Calcd	Found
$CH_2=C(CH_3)(CH_2)_3CH=C(CH_3)CH_2CH(COCH_3)COOC_2H_5$	29085-27-6	103–104 (0.05)	1.4629	266	270
$[CH_2=C(CH_3)(CH_2)_3CH=C(CH_3)CH_2]_2C(COCH_3)COOC_2H_5$	29085-29-8	160–162 (0.01)	1.4847	402	395
$CH_2=C(CH_3)(CH_2)_3CH=C(CH_3)CH_2CH(COCH_3)_2$	29085-32-3	96–98 (0.02)	1.4808	236	234
$[CH_2=C(CH_3)(CH_2)_3CH=C(CH_3)CH_2]_2C(COCH_3)_2$	29085-33-4	150–152 (0.001)	1.4910	372	377
$CH_2=CHCH_2CH(CH_3)CH_2CH=CHCH(CH_3)CH(COCH_3)COOC_2H_5$	29331-11-1	104–105 (0.35)	1.4569	266	265
$CH_2=CHCH_2CH(CH_3)CH_2CH=CHCH(CH_3)CH_2COOC_2H_5$	29331-12-2	74–76 (0.02)	1.4482	224	223
$CH_2=C(CH_3)-CH(CH_3)CH_2CH_2C(CH_3)=C(CH_3)CH_2CH(COCH_3)COOC_2H_5$	29085-31-2	122 (3)	1.4700	294	290

[a] See footnote *a* in Table III.

$PdCl_2(Ph_3As)_2$,[21] $PtCl_2(Ph_3P)_2$,[22] and $Pt(Ph_3P)_4$[22] were prepared by the previously reported methods.

Acetylacetone, ethyl acetoacetate, methyl acetoacetate, diethyl malonate, dimethyl malonate, and malononitrile were purified by distillation under vacuum. Ethyl 2-oxocyclopentanecarboxylate,[23] methyl 2-oxocyclopentanecarboxylate,[23] 2-acetylcyclohexanone,[24] 1,3-cyclohexanedione,[25] cyanoacetamide,[26] 3-oxo-2-methylbutyronitrile,[27] ethyl nitroacetate,[28] and ethyl (phenylsulfonyl)acetate[29] were prepared by the methods described in the literature. Dimethyl 2-acetyl-1,3-propanedicarboxylate and trimethyl 1,1,3-propanetricarboxylate were prepared by reactions of methyl acrylate with methyl acetoacetate and dimethyl malonate, respectively, in the presence of sodium methoxide. 2-Oxocyclohexanecarbaldehyde was synthesized by the reaction of cyclohexanone and methyl formate.[30] 2-Oxocyclododecanecarbaldehyde[31] and ethyl phenylformylacetate were prepared by the same method as employed in the preparation of 2-oxocyclohexanecarbaldehyde.

Purification of 1,3-butadiene was accomplished by vaporization of the liquid diene containing triethylaluminum. Isoprene, 1,3-pentadiene, and 2,3-dimethyl-1,3-butadiene were distilled under argon atmosphere.

General Procedure for Reaction of Active Methylene or Methyne Compounds with 1,3-Dienes.—A 100-ml stainless steel autoclave was charged with an active methylene or methyne compound and catalyst components, followed by cooling with Dry Ice–methanol. After removal of the air within the autoclave under vacuum, 1,3-butadiene was vaporized from the liquid diene containing triethylaluminum to be condensed in the autoclave. The reaction was carried out by stirring at 85°. The reaction mixture was distilled and analyzed by vpc without further treatment.

Reaction of Acetylacetone with 1,3-Butadiene.—A mixture of 0.1 mol of acetylacetone, 0.02 mmol of $PdCl_2(Ph_3P)_2$, 2 mmol of sodium phenoxide, and 0.3 mol of the diene was stirred at 85° for 3 hr. The products consisted of **3c** (0.6 g, 3%), **1c** (12.9 g, 62%), **2c** (5.8 g, 18%), and a residue (0.5 g). Spectroscopic data of the products are as follow. **3c**: ν_{max} 1703 (ketone), 1644, 996, and 915 cm^{-1} (-CH=CH_2); τ 8.7 (m, $-CCH_2C-$), ~8.0 (=CCH_2-CCH_2C=), 8.0 and 7.9 (CH_3CO-), 7.1 (m, -CHCCO-), 6.3 (d, -CHCO-), and 4.0–5.3 (m, olefinic protons). **1c**: ν_{max} 1723, 1703, and 1610 (β diketone), 1639, 993, and 911 (-CH=CH_2), 969 cm^{-1} (trans (-CH=CH-); τ 8.6 (m, $-CCH_2C-$), ~8.0 ($-CH_2CCH_2-$), 8.0 and 7.9 (CH_3CO-), 7.5 (t, $-CH_2CCO-$, keto form), 7.1 (br s, $-CH_2CCO-$, enol form), 6.3 (t, -CHCO-, keto form), 4.6–5.0 (olefinic protons), and −6.7 [s, -C(OH)=CCO-, enol form]. **2c**: ν_{max} 1702 (ketone), 1644, 994, and 912 (-CH=CH_2), 967 cm^{-1} (trans -CH=CH-); τ 8.6 (m, $-CCH_2C-$), ~8.0 (=CCH_2CCH_2C=), 8.0 (s, CH_3CO-), 7.5 (d, $-CH_2CCO-$), and 4.0–5.1 (m, olefinic protons).

Reaction of Ethyl Acetoacetate with Isoprene.—A mixture of 0.1 mol of ethyl acetoacetate, 0.3 mol of isoprene, 0.1 mmol of $PdCl_2(Ph_3P)_2$, and 2 mmol of sodium phenoxide was stirred at 85° for 20 hr. The product consisted of **4a** (17.8 g, 67%), **5a** (11.0 g, 28%), and a residue (0.9 g). The former compound showed the following spectral characteristics: ν_{max} 1740 and 1718 (keto ester), 1652 and 886 cm^{-1} (>C=CH_2); τ 8.8 and 5.9 (t, and q, $-OCH_2CH_3$), ~8.5 ($-CCH_2C-$), 8.4 and 8.3 [2 s, $-C(CH_3)$=C-], ~8.0 (m, =CCH_2CCH_2C=), 7.9 (CH_3CO-), 7.6 (d, $-CH_2CCO-$), 6.5 (t, -CHCO-), 5.4 (s, >C=CH_2), and 4.8 (t, -CH=C<). The latter compound showed following spectral characteristics: ν_{max} 1740 sh and 1712 (keto ester), 1651 and 886 cm^{-1} (>C=CH_2); τ 8.8 and 5.9 (t, and q, $-OCH_2CH_3$), ~8.5 ($-CCH_2C-$), 8.5 [s, $-C(CH_3)$=C-], 8.3 [s, $-C(CH_3)$=C-], ~8.0 (=CCH_2CCH_2C=), 7.9 (s, CH_3CO-), 7.4 (s, $-COCCH_2-$), 5.4 (s, >C=CH_2), and 4.9 (t, -CH=C<).

Reaction of Acetylacetone with Isoprene.—A mixture of 0.1 mol of acetylacetone, 0.3 mol of isoprene, 0.25 mmol of $PdCl_2(Ph_3P)_2$, and 2.5 mmol of sodium phenoxide in 15 ml of benzene was stirred under the same conditions as those of the previous experiment to yield **4c** (15.8 g, 67%) and **5c** (9.0 g, 24%). The former compound showed the following spectral characteristics: ν_{max} 1728 sh, 1700, and 1602 (β diketone), 1649 and 886 cm^{-1} (>C=CH_2); τ ~8.5 ($-CCH_2C-$), ~8.4 [$-(CH_3)C$=C-], 8.0 (=CCH_2-CCH_2C=), 8.0 and 7.9 (s, CH_3CO-), 7.5 (d, $-CH_2CCO$, keto form), 7.1 (s, $-CH_2CCO-$, enol form), 6.3 (t, -CHCO-), 5.4 (s, >C=CH_2), and 4.9 (-CH=C<). The latter compound exhibited the following spectral characteristics: ν_{max} 1699 (ketone), 1651 and 886 cm^{-1} (>C=CH_2); τ ~8.5 ($-CCH_2C-$), 8.6 and 8.3 [2 s, $-C(CH_3)$=C-], ~8.1 (=CCH_2CCH_2C=), 8.0 (s, CH_3CO-), 7.3 (s, $-CH_2CCO-$), 5.4 (s, >C=CH_2), and 4.9 (t, -CH=C<).

Reaction of Ethyl Acetoacetate with 1,3-Pentadiene.—The reaction was carried out under the same conditions as those in the reaction of ethyl acetoacetate with isoprene. The product (8.5 g, 32%) was identified as ethyl 2-acetyl-3,7-dimethyl-4,9-decadienoate: ν_{max} 1742 sh and 1716 (keto ester), 1644, 994, and 912 (-CH=CH_2), and 972 cm^{-1} (trans -CH=CH-); τ 9.2 [d, $-C(CH_3)$], 9.0 [2 d, $-C(CH_3)-$], 8.8 (2 t, $-OCCH_3$), 8.4 (m, =CCCHCC=), 8.1 (m, =CCH_2CCH_2C=), 7.9 and 8.0 (CH_3CO-), 7.1 (m, =CCHCCO-), 6.8 (d, -CHCO-), 5.9 (2 q, $-OCH_2C-$) and 4.0–5.2 (m, olefinic protons). Two kinds of the signals due to acetyl, ethyl, and one of the methyl groups on the side chain indicate that the compound is a mixture of the erythro and threo isomers. Refluxing the product with sodium ethoxide in ethanol gave ethyl 3,7-dimethyl-4,9-decadienoate: ν_{max} 1740 (ester), 1644, 992, and 911 (-CH=CH_2), and 971 cm^{-1} (trans -CH=CH-); τ 9.2 [d, $-C(CH_3)-$], 9.0 [d, $-C(CH_3)-$], 8.8 (t, $-OCCH_3$), 8.5 (m, =CCCHCC=C), 8.0 (m, =CCH_2CCH_2C=), 7.8 (d, $-CH_2CO-$), 7.4 (m, =CCHCCO-), 6.0 (q, $-OCH_2C$), 4.0–5.1 (olefinic protons).

Reaction of Ethyl Acetoacetate with 2,3-Dimethyl-1,3-butadiene.—A mixture of 0.05 mol of ethyl acetoacetate, 0.15 mol of 2,3-dimethyl-1,3-butadiene, 0.25 mmol of $PdCl_2(Ph_3P)_2$, and 2.5 mmol of sodium phenoxide in 15 ml of benzene was stirred at 85° for 20 hr. The product (1.0 g, 7%) was identified as ethyl 2-acetyl-4,5,8,9-tetramethyl-4,9-decadienoate: ν_{max} 1742 and 1720 (keto ester), 1647, 890 cm^{-1} (>C=CH_2); τ 9.0 [d, $-C(CH_3)-$], 8.8 (t, $-OCCH_3$), 8.4 and 8.5 [s, $=C(CH_3)-$], 8.1 (m, =CCCH$_2$CC=), 7.9 (s, CH_3CO-), 7.5 (d, $-CH_2CCO-$), 6.6 (t, -CHCO-), 5.8 (q, $-OCH_2C$), and 5.4 (s, olefinic protons).

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2-(2,7-Octadienyl)cyclohexanone.—A mixture of 150 ml of ethanol, 0.5 g of sodium metal, and 39.8 g of 2-acetyl-2-(2,7-octadienyl)cyclohexanone was heated at 80° for 2 hr. After the usual workup, the product was distilled; the first fraction had bp 110–120° (2 mm), 7.6 g, and the second fraction had bp 168–176° (2 mm), 27.0 g. Redistillations of both fractions gave 2-(2,7-octadienyl)cyclohexanone [bp 116° (3 mm); $n^{25}D$ 1.4809; ν_{max} 1712 (>C=O), 1644, 990, and 910 (-CH=CH_2), and 970 cm^{-1} (trans -CH=CH-)] and ethyl 6-acetyl-8,13-tetradecadienoate [bp 181° (3.5 mm); $n^{25}D$ 1.4635; ν_{max} 1737 (ester), 1713 (>C=O), 1642, 993, and 910 (-CH=CH_2), and 970 cm^{-1} (trans -CH=CH-)], respectively.

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75; mol wt, 206. Found: C, 81.23; H, 10.65; mol wt, 205. *Anal.* Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27; mol wt, 294. Found: C, 73.57; H, 10.19; mol wt, 294.

2-(2,7-Octadienyl)cyclohexanone was also obtained by refluxing an aqueous sodium hydroxide solution of 1-(2,7-octadienyl)-2-oxocyclohexanecarbaldehyde in a 87% yield.

Platinum-Catalyzed Reaction of Acetylacetone with 1,3-Butadiene.—A mixture of 0.1 mol of acetylacetone, 0.5 mmol of $Pt(Ph_3P)_4$, 7 mmol of sodium phenoxide, and 0.3 mol of 1,3-butadiene was stirred at 85° for 16 hr. The product was composed of 3-(1-methylallyl)-2,4-pentanedione (2.0 g, 13%), **1c** (4.5 g, 21%), **3c** (4.8 g, 24%), 3-(2-butenyl)-3-(2,7-octadienyl)-2,4-pentanedione (2.6 g, 10%), and **2c** (3.3 g, 11%). The 1:1 adduct showed the following spectral characteristics: ν_{max} 1722 sh and 1700 (ketone), 1644, 998, and 922 cm^{-1} (-CH=CH_2); τ 9.0 (d, -CCH_3), 8.0 and 7.9 (CH_3CO-), 7.0 (m, =CCH-), 6.4 (d, -CHCO-), 4.8–5.2 (m, CH_2=C-), and 4.0–4.6 (m, -CH=C-) The 1:3 adduct exhibited the following spectral characteristics: ν_{max} 1723 sh and 1702 (ketone), 1643, 991, and 910 (-CH=CH_2), 967 cm^{-1} (trans -CH=CH-); τ 8.6 (m, =$CCCH_2CC$=), 8.3 (d, =CCH_3), ~8.0 (=CCH_2CCH_2C=), 8.0 (CH_3CO-), 7.5 (d, -CH_2CCO-), 4.0–5.2 (m, olefinic protons).

A mixture of 0.1 mol of acetylacetone, 0.5 mmol of $PtCl_2(Ph_3P)_2$, 7 mmol of sodium phenoxide, and 0.3 mol of 1,3-butadiene in 15 ml of benzene was stirred at 85° for 5 hr. The adducts **1c**, **3c**, and **2c** were obtained in 18, 12, and 44% yields, respectively.

Registry No.—2-(2,7-Octadienyl)cyclohexanone, 29331-14-4; ethyl 6-acetyl-8,13-tetradecadienoate, 29331-15-5; 3-(2-butenyl)-3-(2,7-octadienyl)-2,4-pentanedione, 29331-16-6.

Preparation of Alkylmagnesium Fluorides[1]

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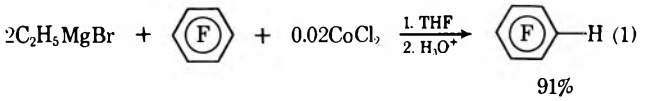
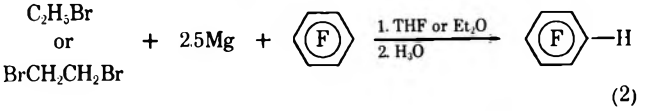
Alkylmagnesium fluorides have been prepared in high yield by the reaction of alkyl fluorides with magnesium in ether solvents in the presence of specific catalysts. The reaction rate was found to depend significantly on the solvent, reaction temperature, and catalyst. The best solvents for the reaction were found to be tetrahydrofuran and 1,2-dimethoxyethane and the best catalyst found was iodine. Under conditions of atmospheric pressure reflux using iodine as a catalyst, *n*-hexylmagnesium fluoride was produced in 90% yield in 14 days in diethyl ether, in 92% yield in 1.2 days in tetrahydrofuran, and in 92% yield in 4 hr in 1,2-dimethoxyethane. Under the most favorable conditions fluorobenzene and benzyl fluoride failed to react with magnesium.

For over half a century organic chemists have been interested in the preparation of organomagnesium fluorides; however, all attempts to prepare and isolate this class of compounds have been uniformly unsuccessful. The first attempt to prepare an organomagnesium fluoride was reported in 1921 by Swarts.[2] He found that the reaction of amyl fluoride with iodine-activated magnesium in diethyl ether after 100-hr reflux produced decane and magnesium fluoride. In 1931 Schiemann and Pillarsky[3] reported that neither fluorobenzene nor its ortho methyl or para nitro derivatives reacted with magnesium to form the corresponding Grignard reagent. The same year Gilman and Heck[4] reported that a small quantity of biphenyl was formed when fluorobenzene was heated with magnesium at 300° for 200 hr in a sealed tube without solvent. When fluorobenzene was sealed in a tube with activated magnesium–copper alloy[5] in diethyl ether at room temperature for 6 months, the reaction mixture gave a negative color test[6] for the presence of an active organometallic compound; however, at the end of 18 months the color test was positive. Several attempts were made by Bernstein and coworkers[7] to prepare a Grignard reagent from benzyl fluoride. At reflux temperature in diethyl ether, no reaction took place. Addition of an iodine crystal or of phenylmagnesium bromide failed to initiate reaction. Under more vigorous conditions in di-*n*-butyl ether, polymerization of the benzyl fluoride occurred. While ordinary magnesium gave no reaction, bibenzyl was obtained from the reaction of benzyl fluoride with activated magnesium in diethyl ether at 100° for 10 days in an autoclave. Thus all attempts to prepare fluoro Grignard reagents were frustrated either by a lack of reaction between the organo fluorides and magnesium or the formation of coupling product.

During our study the possible intermediacy of perfluoroarylmagnesium fluorides was indicated by the reaction of perfluoroaryl compounds with 2 molar equiv of ethylmagnesium bromide and a catalytic amount of certain transition metal halides in tetrahydrofuran[8] (eq 1) and from the reaction of hexafluorobenzene with





magnesium and an equal molar amount of an entrainer such as ethyl or ethylene bromide in tetrahydrofuran

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(2) F. Swarts, *Bull. Soc. Chim. Belg.*, **30**, 302 (1921).
(3) G. Schiemann and R. Pillarsky, *Chem. Ber.*, **64b**, 1340 (1931).
(4) H. Gilman and L. H. Heck, *J. Amer. Chem. Soc.*, **53**, 377 (1931).
(5) H. Gilman and N. B. St. John, *Recl. Trav. Chim. Pays-Bas*, **49**, 717 (1930).
(6) H. Gilman and F. Schulze, *J. Amer. Chem. Soc.*, **47**, 2002 (1925).
(7) J. P. Bernstein, J. S. Roth, and W. T. Miller, *ibid.*, **70**, 2310 (1948).
(8) W. L. Respess and C. Tamborski, *J. Organometal. Chem.*, **18**, 263 (1969).

or diethyl ether[9] (eq 2). The intermediacy of a fluoro Grignard compound was indicated by hydrolysis of the reaction product to produce pentafluorobenzene and by the reaction of the product with an organochlorosilane. However, no attempt was made to identify or isolate the possible intermediate fluoro Grignard compound.

In two preliminary communications we have reported the preparation of heretofore unknown hexylmagnesium fluoride in tetrahydrofuran by the reaction of hexyl fluoride with magnesium in the presence of suitable catalysts at reflux temperature[1] (eq 3) and the

$$RF + Mg \xrightarrow[\text{catalyst}]{THF} RMgF \quad (3)$$

preparation of both aliphatic and aromatic fluoro Grignard reagents by the reaction of dialkyl- and diarylmagnesium compounds with metal halides such as BF_3 (eq 4), R_2AlF, etc.[10] The present report describes

$$3R_2Mg + BF_3 \longrightarrow 3RMgF + R_3B \quad (4)$$

an investigation of the scope of the reaction represented by eq 3 with respect to the nature of the R group, the solvent, and the catalyst in an attempt to arrive at the optimum conditions for preparing fluoro Grignard compounds.

Experimental Section

All operations were carried out either in a Kewaunee nitrogen-filled glove box equipped with a recirculating system to remove oxygen and moisture or on the bench using typical Schlenk tube and syringe techniques.[11] All glassware was flash flamed and flushed with nitrogen prior to use. Triply sublimed magnesium (Dow Chemical) turnings and reflux conditions were employed in all syntheses except when stated otherwise.

Instrumentation.—All infrared spectra were obtained using a Perkin-Elmer 621 high resolution grating spectrophotometer and cesium iodide or potassium iodide absorption cells. Proton magnetic resonance spectra were obtained using a Varian A-60 magnetic resonance spectrometer (TMS standard). Glpc analyses were carried out using an F & M Model 720 gas chromatograph using 3-ft Polypak 2 columns (octane or toluene used as internal standard). Organometallic supernatant solutions were withdrawn at appropriate time intervals and quenched in a septum sealed bottle containing saturated $MgSO_4$ solution. The organic layer was subsequently analyzed by glpc for determination of per cent yield and per cent reaction.

Chemicals.—*n*-Hexyl fluoride was obtained from Columbia Organics. Its purity was checked by glpc analysis and found to be at least 99% pure. Fluorobenzene was obtained from Eastman Organics, benzyl fluoride from Pierce Chemical Co., and ethyl bromide and ethylene bromide (analytical grade) from Baker Chemicals. Gaseous methyl and ethyl fluorides were obtained from Pierce Chemical Co. All of the above were dried using molecular sieve 4A and employed without further purification.

Analytical grade iodine and bromine were obtained from Baker Chemical. Cobalt chloride and sodium iodide (Baker analyzed) were made anhydrous by heating under vacuum. Triply sublimed magnesium turnings (Dow Chemicals) and magnesium powder (Fisher Scientific) were dried under vacuum prior to use.

Anhydrous diethyl ether, tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), and *N,N,N′,N′*-tetramethylethylenediamine (TMED) were distilled from lithium or sodium aluminum hydride, and triethylamine (TEA) from calcium hydride prior to use.

Elemental Analyses.—Elemental analyses were carried out on hydrolyzed samples of the organometallic supernatant solution. Total alkalinity analysis, which gave the concentration of basic magnesium (Mg_B) bonded to carbon, was determined by adding a known amount of acid and back-titrating with standard base using methyl red as an indicator.[12] The same sample was then analyzed for total magnesium (Mg_T) by conventional EDTA complexometric titration at pH 10 using Eriochrome Black T as an indicator; occasionally back-titration with zinc acetate was applied for sharper end points. Chloride, bromide, and iodide were determined by potentiometric titration. The same sample was then analyzed for fluoride by the method described by Hogen and Tortoric.[13]

Preparation of Hexylmagnesium Fluoride from Hexyl Fluoride and Magnesium in Tetrahydrofuran.—The standard procedure used for the preparation of hexylmagnesium fluoride is as follows. A weight of 2.5–5.0 g of magnesium turnings and a certain amount of solid activator (*e.g.*, $CoCl_2$, I_2) were placed in a 100-ml, one-neck flask, with a side arm equipped with a three-way Teflon stopcock. To the neck was attached a water condenser and to the flask was added a magnetic stirring bar. Then 50–70 ml of freshly distilled THF, 2–3 ml of hexyl fluoride, and 2–3 ml of internal standard (toluene or octane) were added *via* syringe through the side-arm stopcock under strong nitrogen flow. The mixture was allowed to react at reflux temperature for a specified period of time. Liquid entrainers (C_2H_5Br, $BrCH_2CH_2Br$, or Br_2) were first dissolved in THF and added dropwise to the reaction mixture at reflux temperature. In some cases the magnesium was first activated by reaction with butyllithium or ethyl bromide in an appropriate solvent. The solution was then decanted prior to reaction.

A. Without Activator (Reaction 1).—Hexyl fluoride (3 ml, 23 mmol) was allowed to react with magnesium (3 g, 123 mg-atoms) in 60 ml of THF for 13 days. After standing, analysis of the clear supernatant solution showed no soluble magnesium and the ratio of hexyl fluoride and octane was constant during the reaction.

B. Butyllithium as Activator (Reaction 2).—Magnesium (5 g, 206 mg-atoms) was activated by stirring with 15 ml of butyllithium–hexane solution (1.6 *N*) in 250 ml of distilled hexane for 1 day. Then the solution was decanted and hexyl fluoride (3 ml, 23 mmol) and THF (60 ml) were added. Analysis indicated that the solution contained no magnesium after 9 days of stirring at room temperature or after 3 days of additional reflux.

C. Bromine as Activator (Reaction 5).—Hexyl fluoride (3 ml, 23 mmol) was allowed to react with magnesium (3 g, 123 mg-atoms) in 50 ml of THF with bromine (0.1 ml) as activator. A light brown solution was formed after 5 days. *Anal.* Mg_T, 0.529 *N*; F, 0.41 *N*; Br, 0.073 *N* (97% reaction, 72% yield.)

D. Ethylene Bromide as Activator (Reaction 6).—Hexyl fluoride (5 ml, 38 mmol) was allowed to react with magnesium powder (3 g, 123 mg-atoms) in 75 ml of THF with ethylene bromide (0.1 ml) as activator for 22 days. *Anal.* Mg_B, 0.879 *N*; Mg_T, 0.699 *N*; F, 0.578 *N*; Br, 0.011 *N* (100% reaction, 42% yield).

E. Ethyl Bromide as Activator (Reaction 7).—Hexyl fluoride (3 ml, 23 mmol) was allowed to react with magnesium (3 g, 123 mg-atoms) in 50 ml of THF using ethyl bromide as activator.

Reaction 7a (1 drop of ethyl bromide was used). *Anal.* after 22 days. Mg_B, 0.458 *N*; Mg_T, 0.288 *N*; F, 0.199 *N*; Br, 0.02 *N* (100% reaction, 94% yield).

Reaction 7b [1 ml (13 mmol) of ethyl bromide was used]. *Anal.* after 8 days. Mg_B, 0.633 *N*; Mg_T, 0.550 *N*; F, 0.266 *N*; Br, 0.201 *N* (95% reaction, 92% yield).

Reaction 7c [2 ml (26 mmol) of ethyl bromide was used]. *Anal.* after 8 days. Mg_B, 0.936 *N*; Mg_T, 0.850 *N*; F, 0.257 *N*; Br, 0.567 *N* (99% reaction, 97 yield).

Reaction 7d [magnesium powder (4 g, 165 mg-atoms) was activated by ethyl bromide (4 ml, 53 mmol) followed by decantation of ethylmagnesium bromide solution]. *Anal.* after 8.5 days (63% reaction, 51% yield). *Anal.* after 20 days. Mg_B, 0.574 *N*; Mg_T, 0.409 *N*; F, 0.282 *N*; Br, 0.012 *N* (96% reaction, 63% yield).

F. Anhydrous Sodium Iodide as Activator (Reaction 3).—Hexyl fluoride (3 ml, 23 mmol) was allowed to react with magnesium (5 g, 123 mg-atoms) in 60 ml of THF using sodium iodide (0.17 g, 1.1 mmol) as activator. No reaction took place after 11 days.

G. Anhydrous Cobalt Chloride as Activator (Reaction 4).—

(9) W. L. Respess, J. P. Ward, and C. Tamborski, *J. Organometal. Chem.*, **19**, 191 (1969).

(10) E. C. Ashby and J. A. Nackashi, *ibid.*, **24**, C17 (1970).

(11) D. F. Shriver, "The Manipulation of Air Sensitive Compounds," McGraw-Hill, New York, N. Y., 1969.

(12) H. Gilman, E. Zoellner, and J. Dickey, *J. Amer. Chem. Soc.*, **51**, 1576 (1929).

(13) J. M. Hogen and F. Tortoric, *Anal. Chem.*, **39**, 221 (1967).

Hexyl fluoride (3 ml, 23 mmol) was allowed to react with magnesium (3 g, 123 mg-atoms) in 50 ml of THF using cobalt chloride (0.06 g, 0.5 mmol) as activator for 21 days. *Anal.* Mg_B, 0.504 *N*; Mg_T, 0.389 *N*; F, 0.313 *N*; Cl, 0.011 *N* (98% reaction, 95% yield).

H. Iodine as Activator (Reaction 8).—Hexyl fluoride (3 ml, 23 mmol) was allowed to react with magnesium (3 g, 123 mg-atoms) in 70 ml of THF using iodine as the activator.

Reaction 8a [0.025 g (0.1 mmol) of iodine was used]. No reaction took place even after 24 days.

Reaction 8b [0.068 g (0.3 mmol) of iodine was used]. *Anal.* after 5 days. Mg_B, 0.338 *N*; Mg_T, 0.285 *N*; F, 0.232 *N*; I, 0.004 *N* (97% reaction, 95% yield).

Reaction 8c [0.26 g (1.0 mmol) of iodine was used]. *Anal.* after 5 days. Mg_B, 0.380 *N*; Mg_T, 0.340 *N*; F, 0.306 *N*; I, 0.01 *N* (100% reaction, 97% yield).

When reaction 8c using 0.26 g of iodine was repeated in 40 ml of THF for a longer period of time (reaction 8d), the yield did not decrease over a 6–14-day reflux period. *Anal.* Mg_B, 0.511 *N*; Mg_T, 0.473 *N*; F, 0.489 *N*; I, 0.014 *N* (100% reaction, 94% yield).

Reaction 8e [0.33 g (1.3 mmol) of iodine was used and the reaction was carried out in 60 ml of THF at 24°]. *Anal.* after 36 days. Mg_B, 0.306 *N*; Mg_T, 0.285 *N*; F, 0.256 *N*; I; 0.008 *N* (95% reaction, 93% yield).

I. Hexylmagnesium Fluoride Solution as Activator (Reaction 9).—Hexyl fluoride (3 ml, 23 mmol) was allowed to react with magnesium (3 g, 123 mg-atoms) in 60 ml of THF using 10 ml of 0.285 *N* hexylmagnesium fluoride solution (from reaction 8b). *Anal.* after 12 days. Mg_B, 0.390 *N*; Mg_T, 0.264 *N*; 0.181 *N*; I, 0.002 *N* (97% reaction, 95% yield).

Preparation of Hexylmagnesium Fluoride from Hexyl Fluoride in Other Solvents.—The method used for the preparation of hexylmagnesium fluoride in othr solvents is similar to that used for the preparation in THF.

A. Diethyl Ether (Reaction 10).—Hexyl fluoride (3 ml, 23 mmol) was allowed to react with magnesium (3 g, 123 mg-atoms) in 70 ml of diethyl ether using iodine (0.251 g, 0.99 mmol) as activator. *Anal.* after 13 days. Mg_B, 0.346 *N*; Mg_T, 0.274 *N*; F, 0.195 *N*; I, 0.03 *N* (88% reaction, 83% yield).

B. Dimethoxyethane (Reaction 11).—Hexyl fluoride (3 ml, 23 mmol) was allowed to react with magnesium (3 g, 123 mg-atoms) in 55 ml of DME using iodine (0.186 g, 0.73 mmol) as activator. *Anal.* after 7 hr. Mg_B, 0.327 *N*; Mg_T, 0.334 *N*; F, 0.295 *N*; I, 0.019 *N* (99% reaction, 95% yield).

C. *N,N,N',N'*-Tetramethylethylenediamine (Reaction 12) and Triethylamine (Reaction 13).—Hexyl fluoride (3 ml, 23 mmol) was allowed to react with magnesium (3 g, 123 mg-atoms) in 50 ml of TMED with iodine (0.20 g, 0.7 mmol) and in a separate experiment using 60 ml of TEA with iodine (0.30 g, 1.2 mmol) for 7 hr. Analyses showed in each case a negligible amount of magnesium in solution, and the formation of hexene.

Attempted Preparation of Phenylmagnesium Fluoride.—Fluorobenzene (3 ml, 32 mmol) was allowed to react with magnesium (3 g, 123 mg-atoms) in 75 ml of THF using iodine (0.36 g, 1.4 mmol) as activator (reaction 14a). After 14 days, analysis showed negligible reaction. The reaction also did not take place in 60 ml of DME using iodine (0.34 g, 1.3 mmol) as activator after 8 days (reaction 14b).

Attempted Preparation of Benzylmagnesium Fluoride (Reaction 15).—Benzyl fluoride (3 ml, 20.8 mmol) was allowed to react with magnesium (3 g, 123 mg-atoms) in 75 ml of THF using iodine (0.22 g, 0.87 mmol) as activator. After 13 days, analysis showed negligible reaction.

Preparation of Ethylmagnesium Fluoride (Reaction 16a).—Ethyl fluoride (4.9 g, 102 mmol) was passed through a tube of molecular sieve (4A) and then introduced through a side arm at the bottom of a Dry Ice condenser into the reaction flask containing magnesium (3 g, 123 mg-atoms), iodine (0.23 g, 0.9 mmol), and 75 ml of THF. *Anal.* after 2.5 days. Mg_B, 0.339 *N*; Mg_T, 0.300 *N*; F, 0.278 *N*; I, 0.014 *N* (36% yield).

Preparation of Methylmagnesium Fluoride and Other Alkylmagnesium Fluorides by Autoclave Techniques.—The preparation of methylmagnesium fluoride will illustrate the method employed. A weighed amount of magnesium was placed in the autoclave. The autoclave was flash flamed under nitrogen and kept under vacuum for 3 hr. Then the apparatus was cooled with Dry Ice–acetone and the desired solvent containing a certain amount of iodine was introduced under a nitrogen flow. After the solvent was cooled, methyl fluoride was passed through a tube of molecular sieve and introduced into the autoclave. The autoclave was then sealed and the reaction carried out at the desired temperature with stirring.

When the reaction was carried out with excess methyl fluoride (32.4 g, 953 mmol), magnesium (5 g, 205 mg-atoms), and iodine (0.57 g, 2.2 mmol) in 100 ml of THF at 70° for 5 days (reaction 17a), analysis showed negligible magnesium in solution and glpc analysis of the solution indicated more than 25 peaks.

The reaction was then carried out with approximately equimolar quantities of methyl fluoride (8 g, 235 mmol) and magnesium (5 g, 205 mg-atoms) plus iodine (0.38 g, 1.5 mmol) in 100 ml of THF at 60° for 3 days (reaction 17b). Analyses showed the resultant solution to be 0.0295 *N* in Mg_B and 0.0175 *N* in Mg_T. Glpc analysis of the solution showed 10 peaks.

A similar reaction (reaction 17c) was carried out in 60 ml of DME with methyl fluoride (10 g, 290 mmol), magnesium (10 g, 410 mg-atoms), and iodine (0.47 g, 1.9 mmol) at 60° for 4 hr. *Anal.* Mg_B, 0.910 *N*; Mg_T, 0.519 *N*; 0.070 *N*; I, 0.039 *N*.

The reaction was then carried out under milder conditions with methyl fluoride (6.8 g, 200 mmol), magnesium (10 g, 410 mg-atoms), and iodine (0.54 g, 2.1 mmol) in 75 ml of THF at room temperature for 1.5 days (reaction 17d). *Anal.* Mg_B, 2.21 *N*; Mg_T, 2.23 *N*; F, 2.24 *N*; I, 0.03 *N*.

The reaction was also carried out in 70 ml of diethyl ether with methyl fluoride (6.7 g, 197 mmol), magnesium (10 g, 410 mg-atoms), and iodine (0.50 g, 1.8 mmol) at room temperature for 3 days (reaction 17e). Analyses showed it to be 0.36 *N* in Me_2Mg and to have a negligible F concentration.

An attempt was also made to prepare ethylmagnesium fluoride at room temperature in an autoclave (reaction 16b) by reaction of ethyl fluoride (7.48, 154 mmol), magnesium (10 g, 410 mg-atoms), and iodine (0.62 g, 2.4 mmol) in 75 ml of diethyl ether for 2 days. *Anal.* Mg_B, 0.270 *N*; Mg_T, 0.173 *N*; F, 0; I, 0.03 *N*.

An attempt was made (reaction 18) to prepare hexylmagnesium fluoride in diethyl ether at 90° in an autoclave by reaction of hexyl fluoride (2 ml, 15 mmol), magnesium (4, g, 164 mg-atoms), and iodine (0.21 g, 0.82 mmol) for 24 hr. *Anal.* Mg_B, 0.122 *N*; Mg_T, 0.0726 *N*; F, 0.0165 *N*; 0.009 *N* (98% reaction).

Stability of Alkylmagnesium Fluorides.—A THF solution of freshly prepared ethylmagnesium fluoride (reaction 16a) gave the following analysis: 0.339 *N* in Mg_B, 0.300 *N* in Mg_T, and 1.12 *N* in Mg_B–Mg_T. After the solution stood for 4 months, the analysis was 0.325 *N* in Mg_B, 0.298 *N* in Mg_T, and 1.09 *N* in Mg_B–Mg_T.

A diethyl ether solution of freshly prepared hexylmagnesium fluoride gave the following analysis: 1.290 *N* in Mg_B, 1.188 *N* in Mg_T, and 1.08 *M* in Mg_BOMg_T. When 15 ml of the solution was heated at 85° for 15 days in a sealed tube, the following analysis was obtained: 1.514 *N* in Mg_B, 1.316 *N* in Mg_T, and 1.15 *N* in Mg_B–Mg_T.[14]

A THF solution of hexylmagnesium fluoride was 1.086 *N* in Mg_B, 0.998 *N* in Mg_T, and 1.09 *N* in Mg_B–Mg_T. After the solution stood for 4 months at room temperature the solution analyzed as 1.051 *N* in Mg_B, 1.044 *N* in Mg_T, and 1.01 *N* in Mg_B–Mg_T.

Results and Discussion

For the direct synthesis of difficultly formed Grignard reagents three modifications of the usual procedure for reacting an organic halide with magnesium have been employed: (1) use of a stronger coordinating solvent, (2) application of higher reaction temperatures, and (3) activation of the magnesium metal.[15] The third method consists of activation of the magnesium by reduction of the size of the metal particles or by chemical reaction. The Gilman catalyst (a combination of magnesium and iodine) is a well-known example of chemical activation. Ethyl bromide or ethylene bromide is also used in catalytic amount to activate the magnesium surface and in molar quantities as an entrainer. Using

(14) The differences in concentration observed is probably due to evaporation of ether solvent during the handling of these highly volatile solutions under conditions of rapid nitrogen purge.

(15) E. Pearson, D. Cowan, and J. D. Becker, *J. Org. Chem.*, **24**, 504 (1959).

TABLE I

PREPARATION OF HEXYLMAGNESIUM FLUORIDE[a-c]

Reaction no.	Solvent	Catalyst	Mol % of catalyst[d]	Reaction time, day	% yield[e]	$Mg_B:Mg_T:F$[f]
1	THF	None	0	13	0	
2	THF	*n*-BuLi[g]		9	0	
3	THF	NaI	4.8	11	0	
4	THF	$CoCl_2$	2.1	7	0	
				21	95	1.29:1:0.80
5	THF	Br_2	8	5	72 (97)	···:1:0.92
6	THF	$BrCH_2CH_2Br$	1.1	7.5	88	
				22.5	42 (100)	1.26:1:0.84
7a	THF	C_2H_5Br	2.2	5	0	
				14	87	
				22	94	1.60:1:0.44
7b	THF	C_2H_5Br	58	1.5	86	
				2.5	91	
				8.0	92	1.24:1:0.76
7c	THF	C_2H_5Br	113	1.5	91	
				8.0	96	
				14.0	97	1.30:1:0.91
7d	THF	C_2H_5Br[g]	2.6	8.5	51 (63)	
				20	63 (96)	1.41:1:0.71
8a	THF	I_2	0.4	24	0	
8b	THF	I_2	1.3	1.2	48	1.18:1:0.82
				1.8	71	
				3.8	95	
				5	97	
8c	THF	I_2	4.3	0.3	41	
				0.8	77	
				1.2	92	
				5	97	1.12:1:0.93
8d	THF	I_2	4.3	6	95	
				14	94	1.06:1:1.06
8e	THF	I_2	5.7	3	11	
				13	46	
				20	68	
				28	84	
				36	93	1.07:1:0.92
9	THF	*n*-$C_6H_{13}MgF$[h]	12.5	2	26	
				6	73	
				12	95	1.48:1:0.68
10	$(C_2H_5)_2O$	I_2	4.3	3	11	
				7	36	
				10	61	
				13	83	1.27:1:0.72
11	DME	I_2	3.2	0.2	92	
				0.3	95	1.01:1:0.91
12	TMED[i]	I_2	3.0	0.3	0	
13	TEA[i]	I_2	5.2	0.3	0	

[a] All reactions run at reflux temperatures and using magnesium turnings except reactions 8e at room temperature and reactions 6 and 7d using Mg powder. [b] Mg:RF, 5.4, except in reactions 2 and 6 where Mg:RF = 8.9 and 3.2 respectively. [c] . . . indicate that no measurement was made. [d] Based on organo fluoride. [e] Based on the formation of hexane by glpc analysis. If the per cent yield is different from the per cent extent of reaction by more than 5%, the per cent reaction is given in parentheses. [f] Impurities introduced by catalyst are excluded: Mg_B, total alkalinity; Mg_T, total magnesium; F, fluoride. [g] After magnesium was activated, the solution was withdrawn before adding hexyl fluoride. [h] Hexylmagnesium fluoride (10 ml) from reaction 8b. [i] Dehydrohalogenation occurred.

a combination of all three methods (solvent, temperature, and catalyst), we have been able to prepare for the first time alkylmagnesium fluorides conveniently and in high yields (eq 5). The following facts are most

$$RF + Mg \xrightarrow[\text{ether solvent}]{\text{catalyst}} RMgF \qquad (5)$$

certain evidences for the formation of the alkylmagnesium fluorides. First, elemental analyses show that the solutions produced on reaction of alkyl fluorides and magnesium contains C–Mg, Mg, and F in the ratio of approximately 1:1:1. Second, the formation of the C–Mg bond is indicated by both ir and nmr spectral analysis and by the alkylating properties of the solutions. Third, molecular association studies show a behavior different from that of organomagnesium chlorides, bromides and iodides.

To investigate the effect of solvent, catalyst, temperature, reaction time, etc., on the formation of fluoro Grignard reagents from organo fluorides and magnesium, *n*-hexyl fluoride was allowed to ract with magnesium under a varity of experimental conditions. Hexyl fluoride was chosen for this study since it is a liquid at room temperature and is commercially available. During the reactions to be studied, samples were withdrawn periodically. The yield was calculated from the amount

of hexane formed after hydrolysis as determined by glpc analysis. At the end of the reaction, the solution was subjected to elemental analyses (total alkalinity, EDTA titration, and fluoride and other halide determinations) and in addition, in some cases, ir and nmr spectra were obtained. The results are summarized in Table I.

Without a catalyst, no reaction was observed when hexyl fluoride was allowed to react with magnesium in tetrahydrofuran for 13 days (reaction 1). No reaction occurred even when attempts were made to activate the magnesium by stirring with *n*-butyllithium in hexane overnight before attempting to initiate the reaction (reaction 2). Addition of sodium iodide (reaction 3) or cobalt chloride (reaction 4) had no effect, except after an induction period of 7 days when cobalt chloride was used as a catalyst. Although the reaction is slow, the fluoro Grignard compound was produced in 95% yield after 21 days. Addition of a catalytic amount of bromine (reaction 5), ethylene bromide (reaction 6), ethyl bromide (reaction 7), or iodine (reaction 8) also catalyzed the formation of the fluoro Grignard. In an attempt to decrease the contamination of the product brought about by the addition of a catalyst, hexylmagnesium fluoride from reaction 8b was used as an activator (reaction 9). After 12.5 days, a 95% yield of soluble magnesium product was obtained; however, the reaction was slow and the reaction product exhibited a low Mg:F ratio, 1.0:0.68.

It is interesting to note that no coupling product, dodecane, or octane was observed except when ethylmagnesium bromide was used as the entrainer. On the other hand three unidentified peaks were observed by glpc analysis of a hydrolyzed sample of hexylmagnesium fluoride. Except when magnesium powder was used (reaction 6 and 7d), less than 5% by-product was observed. The amount of by-product did not vary substantially from experiment to experiment regardless of the nature of the catalyst or reaction time.

The best results in THF solvent were obtained when iodine (4%) was used as a catalyst. Hexylmagnesium fluoride (Mg:F, 1.0:0.93) was produced in 92% yield in only 1.2 days (reaction 8c). Iodine is not only the most efficient catalyst studied (Table II), but also the reaction product is less contaminated owing to the unusually low solubility of magnesium iodide in tetrahydrofuran (<3% based on RMgF). For this reason iodine was selected as the catalyst to be used in subsequent studies involving solvent and temperature effects in the preparation of hexyl- and other organomagnesium fluorides.

TABLE II

EFFECT OF CATALYST ON THE REACTION TIME[a]

Reaction no.	Catalyst	Catalyst, %	Time, days
8b	I_2	1.3	3
6	$BrCH_2CH_2Br$	1.1	6
7a	C_2H_5Br	2.2	13
4	$CoCl_2$	2.1	20.5

[a] For 90% reaction of hexyl fluoride with magnesium in THF.

Reference to Table III shows that the solvent and reaction temperature have a dramatic effect on the reaction rate. For the same amount of iodide catalyst used, the time required for 90% reaction at reflux temperature became much less as the solvent was changed from diethyl ether to tetrahydrofuran to 1,2-dimethoxyethane. When the reaction was carried out in tetrahydrofuran at room temperature (24°), the time required for 90% reaction was longer than that required in diethyl ether at reflux temperature (>35°). When the reaction was carried out in diethyl ether at 90°, the rate was similar to that achieved in tetrahydrofuran at reflux temperature. These results clearly indicated that the reaction temperature, and to a lesser extent solvent, plays an important role in the rate of reaction. Attempts to prepare hexylmagnesium fluoride in *N,N,N',N'*-tetramethylethylenediamine and triethylamine failed (reactions 12 and 13). Dehydrohalogenation of hexyl fluoride by these solvents appeared to be a major reaction at reflux temperatures.

TABLE III

EFFECTS OF SOLVENT AND TEMPERATURE ON REACTION RATE[a]

Reaction no.	Solvent	Temp, °C	Time, days
10	$(C_2H_5)_2O$	35	13.5
8c	THF	66	1.2
11	DME	90	<0.2
8e	THF	25	24
18	$(C_2H_5)_2O$	90[b]	<1

[a] For 90% reaction of hexyl fluoride. [b] Only 25% of hexylmagnesium compound is fluoride.

The data in Table IV show that, although reaction time can be substantially shortened by addition of larger amounts of catalyst, a low optimum catalyst concentration exists beyond which only a slight increase in reaction rate is observed.

TABLE IV

EFFECT OF CATALYST CONCENTRATION ON REACTION RATE[a]

Reaction no.	Catalyst	Catalyst, %	Time, days
7a	C_2H_5Br	2.2	17.5
7b	C_2H_5Br	58	2
7c	C_2H_5Br	113	1.4
8a	I_2	0.4	∞
8b	I_2	1.3	3
8c	I_2	4.3	1.2

[a] For 90% reaction of hexyl fluoride.

All attempts to prepare phenyl- and benzylmagnesium fluoride failed (Table V). Even in the presence of iodine as a catalyst, fluorobenzene and benzyl fluoride failed to react with magnesium in tetrahydrofuran during a 13-day reflux period. However methyl- and ethylmagnesium fluoride were successfully prepared in tetrahydrofuran using iodine as activator. Because of the low boiling point of ethyl fluoride (−37.7°), the conventional apparatus using a Dry Ice condenser under conditions of tetrahydrofuran reflux was very inconvenient and only 36% yield of product was obtained owing to the escape of ethyl fluoride during the reaction. Because of this problem the synthesis of methylmagnesium fluoride from methyl fluoride (bp −78°) was carried out in an autoclave. The reaction was carried out using excess methyl fluoride since fluoride could be easily removed from the reaction mixture. A reaction was therefore carried out with excess methyl fluoride (MeF:Mg, 4.6) at 70° for 5 days (reaction 17a). How-

TABLE V

PREPARATION OF ORGANOMAGNESIUM FLUORIDES IN ETHER SOLVENTS USING IODINE AS A CATALYST[a]

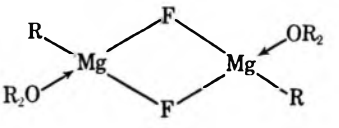
Reaction no.	Organo fluoride	Solvent	Reaction temp, °C	Mg:RF	Mol % of catalyst[b]	Reaction time, day	% yield[c]	$Mg_B:Mg_T:F$[d]
14a	PhF	THF	66	3.8	4.4	14	0	
14b	PhF	DME	90	3.8	4.1	8	0	
15	$PhCH_2F$	THF	66	6.1	4.2	13	0	
16a	C_2H_5F	THF	66	1.2	0.9	2.5	36	1.13:1:0.96
16b	C_2H_5F	THF	25	2.7	1.5	2	13	1.57:1:0
17a	CH_3F	THF	70	0.22	0.2	5	0	
17b	CH_3F	THF	60	0.88	0.6	3	1.2	1.68:1:···[e]
17c	CH_3F	DME	60	1.4	0.6	0.2	19	1.82:1:0.15
17d	CH_3F	THF	25	2.1	1	1.5	95	0.99:1:1.02
17e	CH_3F	$(C_2H_5)_2O$	25	2.1	1	3	13	2.12:1:0
18	n-$C_6H_{13}F$	$(C_2H_5)_2O$	90	11	5.5	1	95	1.77:1:0.25

[a] Reactions were carried out in an autoclave except for reactions 14, 15, and 16a. [b] Based on organo fluoride. [c] Yield determined by titration. [d] Impurities introduced by catalyst are excluded. Mg_B, total alkalinity; Mg_T, total magnesium; F, fluoride. [e] ··· indicated that no measurement was made.

ever, analysis showed negligible magnesium in solution and glpc analysis of the solution showed more than 25 different components to be present. The reaction was then carried out using a slight excess of methyl fluoride (MeF:Me, 1.1) at a lower temperature for 3 days (reaction 17b). Although glpc analysis of the solution showed only 10 peaks, magnesium analyses (M_B and Mg_T) showed that only a very small amount (1.2%) of dimethylmagnesium was formed. The failure of these reactions was probably due to the polymerization of methyl fluoride. The reaction was then carried out in 1,2-dimethoxyethane with excess magnesium at 60° for 4 hr (reaction 17c). Although 19% yield of a CH_3Mg compound was formed, only 15% of this was CH_3MgF. Finally the reaction was successfully carried out with excess magnesium in tetrahydrofuran at room temperature for 1.5 days (reaction 17d). Methylmagnesium fluoride was obtained in 95% yield. Attempts to prepare methyl- and ethylmagnesium fluorides in diethyl ether using autoclave techniques failed (reaction 17e and 16b); the reactions were slow; and only dialkylmagnesium compounds were obtained. Since the preparation of hexylmagnesium fluoride in diethyl ether is extremely slow, the reaction was carried out at 90° in an autoclave. The reaction was indeed accelerated dramatically at higher temperature and gave 95% yield based on soluble magnesium (reaction 18) in 24 hr. However, analyses indicated that the product contained only 25% fluoro Grignard.

The elemental analyses (Tables I and V) show that the products from the reactions of alkyl fluorides and magnesium contain in most cases a ratio of $Mg_B:Mg_T$ of >1 and a Mg:F ratio of <1. The basic magnesium is obtained by acid–base titration (Mg_B for RMgF, 1; R_2Mg, 2) and total magnesium is obtained by EDTA analysis (Mg_T for RMgF, 1; R_2Mg, 1). These results clearly indicate that disproportionation occurs producing a product of low fluoride content and therefore high R_2Mg content. However, disproportionation was not complete in most cases and usually solutions had a $Mg_B:Mg_T$ ratio between 1.3 and 1. It is presumed that disproportionation took place during the formation step since alkylmagnesium fluorides appear to be very stable in solution once formed. Magnesium analyses showed no change in concentration or $Mg_B:Mg_T$ ratio for tetrahydrofuran solutions of ethyl- and hexylmagnesium fluoride after four months. Also hexylmagnesium fluoride in diethyl ether showed no change in the $Mg_B:Mg_T$ ratio after heating at 85° for 15 days in a sealed tube.

The low Mg:F ratios are not surprising since disproportionation in Grignard systems is well known. For example, the attempted preparation of organomagnesium iodides in tetrahydrofuran results in the precipitation of MgI·6THF leaving the dialkyl magnesium compound in solution.[16] The failure of the preparation of methyl- and ethylmagnesium fluoride in diethyl ether is probably due to the complete disproportionation in this solvent resulting in the precipitation of MgF_2 and solution of the dialkylmagnesium compound which is exactly what was observed. Presumably tetrahydrofuran being a more polar solvent solvates the reaction intermediates better during formation of the Grignard compound and lessens disproportionation. Once the fluoro Grignard compound is formed in either diethyl ether or tetrahydrofuran the compound is stable indefinitely. The lack of precipitation of the very insoluble MgF_2 from solution certainly indicates the absence of a Schlenk equilibrium. Molecular association and nmr studies to be reported on in detail elsewhere indicate the composition of primary alkylmagnesium fluorides in either diethyl ether or tetrahydrofuran solution as discrete dimers bound by a double fluorine bridge.



Registry No.—Hexylmagnesium fluoride, 25400-60-6; ethylmagnesium fluoride, 28596-49-8; methylmagnesium fluoride, 420-09-7.

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(16) R. M. Salinger and H. S. Mosher, *J. Amer. Chem. Soc.*, **86**, 1782 (1964).

Preparation of 19-Hydroxy-$\Delta^{4,7}$- and 8,19-Oxido-$\Delta^{4,6}$-3-Keto Steroids

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The deconjugation of 19-hydroxy-$\Delta^{4,6}$-3 ketones **1** and **2** and of 10-methyl-$\Delta^{4,6}$-3 ketone **3** to $\Delta^{4,7}$-3 ketones **7**, **8**, and **9** by treatment with sodium methoxide in dimethyl sulfoxide and subsequent treatment of the basic mixture with aqueous hydrochloric acid is described. Under the same conditions 4-chloro-19-hydroxy-$\Delta^{4,6}$-3 ketone **15** gave an unstable product which was considered to be the free enol **16** and which on treatment with pyridine gave 8,19-oxide **11**. Oxidation of 19-hydroxy-$\Delta^{4,7}$-3 ketones **7** and **8** with ferric chloride also led to 8,19-oxide formation yielding compounds **10** and **11**, respectively. The effect of methanol on the deconjugation of $\Delta^{4,6}$-3 ketone **3** and its 19-hydroxy analog **1** was studied, and it was found that increasing amounts of methanol in the basic reaction mixture inhibit the deconjugation of the former ketone more than that of the latter. It was concluded that during the base treatment the 19-hydroxy group, in its anionic form, assists in the conversion of **1** to the intermediate enol anion **4** by abstracting the proton from the 8β position. The preparation of 4-chloro-19-hydroxy-$\Delta^{4,6}$-3 ketone **15** from 6,19-oxide **12** is described.

Recently in these laboratories[1b] the deconjugation of estra-4,6-diene-3,17-dione and 6-dehydrotestosterone to the corresponding $\Delta^{4,7}$-3 ketones has been accomplished. The deconjugations were affected by deprotonation of the $\Delta^{4,6}$-3 ketones with base in dimethyl sulfoxide and subsequent protonation of the thus formed 3,5,7-trien-3-ol anions by treatment with acid. It appeared interesting to attempt the deconjugation of $\Delta^{4,6}$-3 ketones carrying substituents which may be expected to exert a pronounced effect on the deconjugation itself as well as on the reactivity of the products formed. Accordingly, as a first venture into this rather large field of study, 19-hydroxy-$\Delta^{4,6}$-3 ketones **1** and **2** and 4-chloro-19-hydroxy-$\Delta^{4,6}$-3 ketone **15** (Scheme I) were subjected to deconjugation conditions.

Treatment of $\Delta^{4,6}$-3 ketones **1** and **2** with sodium methoxide in dimethyl sulfoxide and subsequent treatment with excess aqueous hydrochloric acid yielded precipitates consisting essentially of $\Delta^{4,7}$-3 ketones **7** and **8**, respectively. A similar treatment afforded 10-methyl-$\Delta^{4,7}$-3 ketone **9** from $\Delta^{4,6}$-3 ketone **3**, though as a more impure material, from which the pure product could only be isolated by chromatography. By contrast, 4-chloro-19-hydroxy-$\Delta^{4,6}$-3 ketone **15** did not give the corresponding $\Delta^{4,7}$-3 ketone **18** under the above deconjugation conditions but a precipitate which had uv max 305 (sh) and 318 and 333 mμ (sh). After being allowed to stand at room temperature for several hours, the precipitate changed into a material having uv max 255 (major peak) and 298 mμ (minor peak). The uv spectrum thus indicates that the freshly filtered precipitate is 4-chloro-3,5,7-trien-3-ol (**16**), which then on standing converts mainly into 4-chloro-$\Delta^{4,7}$-3-keto steroid **18**.[2] Attempts failed to isolate the latter compound in the pure form.

Attempted acetylation of 3,19-diol **16** with acetic anhydride and pyridine gave 8,19-oxido-$\Delta^{4,6}$-3 ketone **11** and it was also found that this conversion proceeds in pyridine alone. Possibly the free enol **16** yields first the unstable $\Delta^{5,7}$-3 ketone **17** in which the 4-chlorine atom is in an allylic position to the double bond in position 5. Intramolecular substitution with rearrangement[3] would then be expected to lead to a facile expulsion of the chlorine atom by the 19-hydroxy group yielding 8,19-oxide **11** and pyridinium hydrochloride.

Oxidation of 19-hydroxy-$\Delta^{4,7}$-3 ketones **7** and **8** with anhydrous ferric chloride in methanol–tetrahydrofuran (1:1) also led to 8,19-oxide formation yielding **10** or **11**, respectively. An 8,19-oxide, which in subsequent reactions gave 8,19-oxidoprogesterone, has previously been obtained as a by-product on treatment of 3β,5,-14,19-tetrahydroxy-5β,14β-etianic acid with ethanolic hydrogen chloride.[4]

The apparently rather ready interaction of the 19-hydroxy group with the 8-carbon atom in the formation of 8,19-oxides **10** and **11** is paralleled by the interaction of the 19-hydroxy group with the 2-carbon atom in the conversion of 2α-halo-19-acetoxy-$\Delta^{4,6}$-3 ketones to the corresponding 2,19-oxido-$\Delta^{4,6}$-3 ketones under hydrolysis conditions.[5] An interaction of the 19-alkoxy group with the acidic hydrogen atoms in the 2β and 8β position during the base treatment in the deconjugation of the 19-hydroxy-$\Delta^{4,6}$-3 ketones **1** and **2** may then also be expected. That this is so has been indicated by comparative studies on the effect of methanol in the basic mixture on the deconjugation of 19-hydroxy-$\Delta^{4,6}$-3 ketone **1** and its 10-methyl analog **3** to the corresponding $\Delta^{4,7}$-3-ones **7** and **9**, respectively. In the blank reaction the solvent employed consisted of equal volumes of dimethyl sulfoxide and tetrahydrofuran. The latter solvent was then replaced by increasing amounts of methanol in subsequent reactions. Because of the presence of methanol and tetrahydrofuran as cosolvents, the comparative reactions could be carried out at the convenient temperature of 2° (melting point of dimethyl sulfoxide 18°).

The experimental results indicate that increasing proportions of methanol in the cosolvent mixture inhibit the deconjugation. Such an inhibition can be ascribed to a decrease of the basicity of the methoxide anion due to hydrogen bonding[6] with the protic methanol. The experiments indicate in particular that the deconjugation of $\Delta^{4,6}$-3-one **3** is considerably more inhibited by the presence of methanol than the deconjugation of the analogous 19-alcohol **1**. Thus, for example, when the cosolvent mixture contained 60% of methanol, inhibition of the deconjugation of **3** was found to be virtually complete while the deconjugation

(1) (a) Bio-Research Laboratories, Pte. Claire, Quebec, Canada. (b) D. S. Irvine and G. Kruger, *J. Org. Chem.*, **35**, 2418 (1970).

(2) H. Mori, *Chem. Pharm. Bull.*, **10**, 429 (1962), and references therein; 4-chlorotestosterone acetate also has uv max 255 mμ.

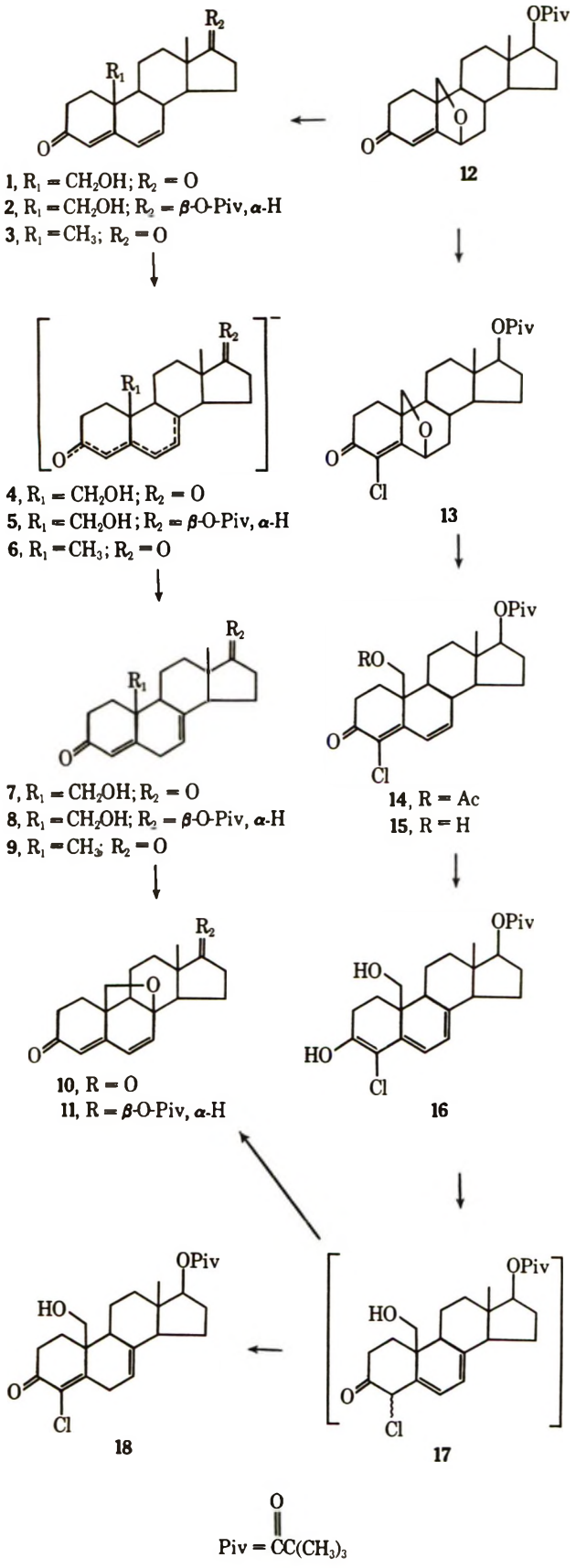
(3) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953, pp 589, 596.

(4) K. Otto and M. Ehrenstein, *J. Org. Chem.*, **26**, 2871 (1961).

(5) G. Kruger and A. Verwijs, *ibid.*, **35**, 2415 (1970).

(6) A. J. Parker, *Quart. Rev., Chem. Soc.*, **16**, 163, 175 (1962), and references therein.

SCHEME I



of **1** was only moderately inhibited and 4,7-diene **7** was still the major product (see Experimental Section). The difference in degree of inhibition by methanol may be rationalized by the assumption that the 19-alkoxide anion of **1**, which can be expected to form even in the presence of relatively large amounts of methanol, accepts the proton from the 8β position by intramolecular abstraction. Alternately the 19-alkoxide anion may first remove the more acidic[7] 2β proton to yield the corresponding 2,4,6-trien-3-ol anion. Subsequent successive intramolecular migration of the 19-hydroxy proton to the anionic 3-oxygen atom of the latter and of the 8β proton to the 19-oxygen atom could then yield the thermodynamically[8] more stable 3,5,7-trien-3-ol anion **4**. In the 10-methyl-$\Delta^{4,6}$-3-one **3**[8] no such intramolecular proton abstraction or transport is possible and thus considerably more basic conditions are required for its conversion to the 3,5,7-trien-3-ol anion **6**.

The preparation of the 4-chloro-19-hydroxy-$\Delta^{4,6}$-3 ketone **15** commenced with the 6,19-oxido-Δ^{4}-3 ketone **12**.[5] Treatment with sulfuryl chloride and collidine in carbon tetrachloride at elevated temperature gave the 4-chloro derivative **13**. Previously steroidal Δ^{4}-3 ketones have been converted in good yield to the 4-chloro analogs with sulfuryl chloride in pyridine at or below room temperature.[2] The 6,19-oxide **12**, however, gave largely starting material under these conditions even when the reaction temperature was increased to 70°. As previously noticed[2] part of the sulfuryl chloride is consumed in side reactions, and it thus appeared that these side reactions became the predominant reaction. It was assumed that it was the pyridine present in the reaction which was responsible for the consumption of the sulfuryl chloride and for this reason the less reactive collidine was used. Very little reaction took place when, in an effort to obtain 19-acetate **14**, 4-chloro-6,19-oxide **13** was treated with acetic anhydride and *p*-toluenesulfonic acid under conditions which readily brought about the conversion of **12** to **2**; when, however, the amount of *p*-toluenesulfonic acid was increased tenfold the reaction was complete within 10–15 min. Possibly the chlorine atom, by its strong negative inductive effect, makes a neighboring-group participation of the 4,5 double bond during the expulsion of the ethereal oxygen atom at position 6 more difficult. Base-catalyzed hydrolysis of the 19-acetate **14** finally gave the 4-chloro-19-hydroxy-$\Delta^{4,6}$-3 ketone **15**.

The structure of the novel compounds prepared has been supported by their ir, uv, and nmr spectra. Of interest are the signals given by the protons at position 6 and 7 in $\Delta^{4,6}$-3 ketones **2**, **10**, **11**, and **15**. Both protons appear as a singlet in $\Delta^{4,6}$-3 ketone **2**, but as a pair of doublets in 8,19-oxido-$\Delta^{4,6}$-3 ketones **10** and **11**, while the 4-chloro-$\Delta^{4,6}$-3-one **15** reveals the 2 protons as a pair of quartets (ABX system, with H_X being bonded to C-8). Apparently the neighboring oxygen or chlorine atoms in **10**, **11**, and **15** bring about an unequal deshielding of the 2 protons and thus a greater downfield shift for one proton signal than for the other. Both inductive and tautomeric electron displacements may play a role and for this reason it may be difficult to decide as to which of the two protons suffered the greater downfield shift. Also of interest is a comparison of the 19-methylene signals given by the deuteriochloroform solutions of the 19-hydroxy-$\Delta^{4,6}$-3 ketone **2** and of the 19-hydroxy-$\Delta^{4,7}$-3 ketones **7** and **8**. The $\Delta^{4,6}$-3

(7) S. K. Malhotra and H. J. Ringold, *J. Amer. Chem. Soc.*, **86**, 1997 (1964).
(8) S. K. Pradhan and H. J. Ringold, *J. Org. Chem.*, **29**, 601 (1964).

ketone shows the methylene protons as a singlet at 3.87 ppm, which, depending on the noise level of the nmr spectrometer, may be accompanied by two barely observable satellites at J = 11 Hz, while the $\Delta^{4,7}$-3 ketones show these protons as pairs of doublets at 3.83–3.84 ppm, with J = 11 Hz and $\delta_A - \delta_B$ = 0.32 ppm. The rather large $\delta_A - \delta_B$ value of the $\Delta^{4,7}$-3 ketones may be taken as an indication of a more restricted rotation of their 19-hydroxy groups.[9,10] Recent, more detailed nmr studies on 19-hydroxy-Δ^4-3-keto steroids have established values of $\delta_A - \delta_B$ = 0.06 ppm for chloroform solutions and of $\delta_A - \delta_B$ = 0.09–0.15 ppm for pyridine solutions.[10] By comparison, the 8,19-oxido-$\Delta^{4,6}$-3 ketones **10** and **11** show their 19-methylene protons as pairs of doublets centered at 4.06 ppm with J = 9 Hz and $\delta_A - \delta_B$ = 0.25 ppm.

Experimental Section[11]

17β-Pivaloxy-19-hydroxyandrosta-4,6-dien-3-one (2).—A mixture of 10 g of 6,19-oxide 12,[5] 30 ml of acetic anhydride, and 0.1 g of *p*-toluenesulfonic acid was treated at 100° for 40 min whereupon 50 ml of water was added at a slow rate. Extraction with methylene chloride, drying, and evaporation yielded the crude 19-acetate of **2** as a resin. The resin was dissolved in 10 ml of methanol and left to stand at room temperature with 0.05 g of sodium methoxide for 4 hr, whereupon 0.1 ml of glacial acetic acid was added. Evaporation and recrystallization from methanol yielded the analytical sample: mp 191–192°; ir ($CHCl_3$) 3640, 3460 (OH), 1715 (pivalate), 1650 ($\Delta^{4,6}$-3 ketone), 1615 and 1585 cm^{-1} (>C=C<); uv max (EtOH) 283 mμ (ε 26,600); nmr 6.15 (s, 2, C-6, C-7), 5.79 (s, 1, C-4), 4.6 (m, 1, C-17), and 3.86 ppm (s, 2, C-19).

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.37; H, 8.92.

19-Hydroxyandrosta-4,7-diene-3,17-dione (7).—To a solution of 1 g of 1[12] in 10 ml of dimethyl sulfoxide was added 2.0 g of sodium methoxide in one portion. The mixture was stirred briefly under nitrogen and then poured into 60 ml of ice-cold 2 *N* hydrochloric acid with stirring. The precipitate was filtered and washed with water. Digestion with acetone and ethyl acetate yielded 0.70 g of crude 7, uv max (EtOH) 239 mμ (ε 14,700). Recrystallization from methanol yielded the pure product: mp 222–223° (lit.[13] mp 212–214°); uv max (EtOH) 239 mμ (ε 16,400); nmr 5.96 (d, 1, J = 2 Hz, C-4), 5.45 (m, 1, C-7), and 3.84 ppm (d of d, 2, J = 11 Hz, $\delta_A - \delta_B$ = 0.32 ppm,[14] C-19).

17β-Pivaloxy-19-hydroxyandrosta-4,7-dien-3-one (8) was prepared from **2** as above yielding 70% of crude material. Recrystallization from methanol gave the analytical sample: mp 193–194°; uv max (EtOH) 238 mμ (ε 16,300); ir ($CHCl_3$) 3640 (OH), 1715 (pivalate), 1650 (Δ^4-3 ketone), 1615 and 1585 cm^{-1} (>C=C<); nmr 5.95 (d, 1, J = 2 Hz, C-4), 5.3 (m, 1, C-7), and 3.83 ppm (d of d, 2, J = 11 Hz, $\delta_A - \delta_B$ = 0.32 ppm, C-19).

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.82; H, 8.65.

8,19-Oxidoandrosta-4,6-diene-3,17-dione (10).—To 5 g of **7** dissolved in 250 ml of tetrahydrofuran–methanol (1:1) was added 20 g of anhydrous $FeCl_3$. The solution was stirred under nitrogen for 20 min whereupon 250 ml of ethyl acetate and 750 ml of water were added. The ethyl acetate phase was washed with water, dried with sodium sulfate, and concentrated to a thick paste. Filtration yielded 1.67 g of yellow crystals which showed a single spot on thin layer chromatography. Recrystallization from ethyl acetate yielded 0.8 g of the analytical sample: mp 224–226°; uv max (EtOH) 289 mμ (ε 24,400); ir ($CHCl_3$) 1740 (17 ketone), 1655 (conjd ketone), 1619 and 1581 cm^{-1} (>C=C<); nmr 6.40 (d of d, 2, J = 9 Hz, $\delta_A - \delta_B$ = 0.28 ppm, C-6, C-7), 5.74 (s, 1, C-4), 4.06 (d of d, 2, J = 8 Hz, $\delta_A - \delta_B$ = 0.25 ppm, C-19), and 1.12 ppm (s, 3, C-18, 8β-O).

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.43; H, 7.15.

8,19-Oxido-17β-pivaloxyandrosta-4,6-dien-3-one (11).—To 0.8 g of **8** dissolved in 20 ml of tetrahydrofuran was added a freshly prepared solution of 2.4 g of anhydrous $FeCl_3$ in 20 ml of methanol. After 5 min of stirring the mixture was poured into 400 ml of 2 *N* aqueous hydrochloric acid. Extraction with benzene, evaporation, and recrystallization of the residue from methanol yielded 0.116 g of the analytical sample: mp 195.5–196°; uv max (EtOH) 290 mμ (ε 26,880); ir ($CHCl_3$) 1720 (pivalate), 1660 (conjd ketone), and 1615 cm^{-1} (>C=C<); nmr 6.33 (d of d, 2, J = 8 Hz, $\delta_A - \delta_B$ = 0.27 ppm, C-6, C-7), 5.72 (s, 1, C-4), 4.06 (d of d, 2, J = 8 Hz, $\delta_A - \delta_B$ = 0.25 ppm, C-19), and 1.05 ppm (s, 3, C-18, 8β-O).

Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 74.71; H, 8.27.

4-Chloro-6,19-oxido-17β-pivaloxyandrost-4-en-3-one (13).—To a solution of 8 g of 12,[5] warmed at 50°, in 16 ml of carbon tetrachloride and 8 ml of *sym*-collidine was added over 4 min and with stirring a solution of 16 ml of redistilled sulfuryl chloride in 32 ml of carbon tetrachloride. Stirring was continued for another 8 min whereupon the mixture was poured into 48 ml of methylene chloride and 48 ml of 2 *N* aqueous hydrochloric acid. The organic phase was extracted four times with aqueous hydrochloric acid and then with water. Concentration to a thick paste and filtration yielded 3.8 g of off-white crystals. Recrystallization from methanol yielded the analytical sample: mp 212–214°; uv max (EtOH) 252 mμ (ε 13,450); ir ($CHCl_3$) 1720 (pivalate), 1690 and 1660 cm^{-1} (Δ^4-3 ketone); nmr 3.92 (d of d, 2, J = 8 Hz, $\delta_A - \delta_B$ = 0.64 ppm, C-19), and 0.90 ppm (s, 3, C-18).

Anal. Calcd for $C_{24}H_{33}O_4Cl$: C, 68.54; H, 7.89; Cl, 8.42. Found: C, 68.74; H, 7.98; Cl, 8.68.

4-Chloro-17β-pivaloxy-19-hydroxyandrosta-4,6-dien-3-one (15).—A solution of 3 g of **13** and 3 g of paratoluenesulfonic acid in 15 ml of acetic anhydride was left to stand at 100° under nitrogen for 10 min whereupon it was poured into 150 ml of water and stirred for 1 hr. The aqueous phase was decanted from the viscous resin, the resin was dissolved in benzene, and the solution was stirred under nitrogen with 1 vol of 50% aqueous potassium hydroxide for 4 hr in an effort to destroy residual amounts of acetic anhydride. The benzene phase was dried with sodium sulfate and evaporated at reduced pressure. The residue, consisting largely of 19-acetate **14**, was dissolved in 30 ml of methanol and left to stand with 0.3 ml of 50% aqueous potassium hydroxide under nitrogen for 1 hr whereupon 0.3 ml of glacial acetic acid was added and the mixture was concentrated to a thick paste. Filtration gave 1.3 g of off-white crystals which after one recrystallization from methanol gave 1.0 g of **15**, mp 220–228°. The analytical sample had mp 232–233°; uv max (EtOH) 298 mμ (ε 26,700); ir ($CHCl_3$) 3640, 3500 (OH), 1720 (pivalate), 1675 (conjd ketone), and 1615 cm^{-1} (>C=C<); nmr 6.53 (d of q, 2, J_{AB} = 10, J_{AX} = 2, J_{BX} = 1.5 Hz, $\delta_A - \delta_B$ = 0.53 ppm, C-6, C-7), and 3.85 ppm (s, 2, C-19).

Anal. Calcd for $C_{24}H_{33}O_4Cl$: C, 68.54; H, 7.89; Cl, 8.42. Found: C, 68.22; H, 7.93; Cl, 8.47.

Preparation of Enol 16 and Its Conversion to 8,19-Oxide 11.—The conditions above used for the deconjugation of 4,6-diene **1** to **7** gave, when applied to 500 mg of 4-chloro-4,6-diene **15**, an acidic aqueous suspension, which after filtration and brief drying at high vacuum at room temperature for 20 min yielded enol **16** having uv max (MeOH) 305 (sh), 318 (major peak), and 333 mμ (sh). On standing of 10 mg of the enol under nitrogen for 10 hr a product was obtained having uv max (MeOH) 255 (major peak), 285 (sh), 298 (minor peak), 318 (sh), and 333 mμ (sh). The remainder of the freshly prepared enol **16** was left to stand in 15 ml of pyridine under nitrogen at room temperature for 10 hr. Dilution with water, extraction with benzene, and chromatographic separation of the benzene solution on silica gel gave, after elution with benzene–ethyl acetate (10:1), evaporation, and digestion of the residue with methanol, 90 mg of 8,19-oxide **11**, mp 186–188°, the infrared spectrum of which was identical with that of the product prepared by oxidation of **8** with ferric

(9) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 90–93.

(10) T. Takahashi, *Agr. Biol. Chem. (Tokyo)*, **27**, 633 (1963); *Tetrahedron Lett.*, No. 11, 565 (1964).

(11) Melting points were determined with a Thomas-Hoover apparatus and are corrected. Infrared spectra were determined with a Perkin-Elmer spectrophotometer, Model 21; nmr spectra were determined in deuteriochloroform with a Varian A-60 spectrometer; chemical shifts are reported in parts per million downfield from tetramethylsilane.

(12) K. Heusler, J. Kalvoda, Ch. Meystre, H. Ueberwasser, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, **18**, 464 (1962).

(13) J. F. Bagli, P. R. Morand, K. Wiesner, and R. Gaudry, *Tetrahedron Lett.*, No. 8, 387 (1964).

(14) Reference 9, p 43.

chloride. Recrystallization from methanol gave the pure sample, mp 195–196°.

Treatment of the free enol **16** with pyridine–acetic anhydride (3:1) instead of pyridine alone gave an essentially identical crude product as evidenced by its ultraviolet spectrum and by thin layer chromatography. Isolation of pure 8,19-oxide **11** was accomplished by chromatography and recrystallization, while identity was established by comparison of infrared spectra.

Deconjugation of 1 and 3 in the Presence of Methanol.—A mixture of 4 g of sodium methoxide, 10 ml of dimethyl sulfoxide, and 10 ml of cosolvent, consisting of varying amounts of methanol and tetrahydrofuran, was stirred in an ice bath and in an atmosphere of prepurified nitrogen until it had cooled down to a temperature of 2–3°. A solution of 1.66 mmol of **1** (500 mg) or of **3** (473 mg) in a mixture of 10 ml of dimethyl sulfoxide and 10 ml of cosolvent was cooled to 2° and then added to the basic reaction mixture in one portion. The temperature of the stirred mixture was maintained at 2–3° for 5 min whereupon 100 ml of benzene and a freshly prepared mixture of 20 ml of concentrated hydrochloric acid and 40 g of ice was added in quick succession. The mixture was stirred for 45 min in a water bath having a temperature of 20°; 10 ml of ethyl acetate and 140 ml of water were then added. The organic phase was extracted five times with 50 ml of water, dried with sodium sulfate, and evaporated at reduced pressure. The residue, which had been freed from all traces of benzene at high vacuum, was dissolved in methanol and its uv spectrum was recorded with a Unicam Sp 800 spectrophotometer. The percentage of $\Delta^{4,7}$-3 ketone in the mixture of $\Delta^{4,7}$- and $\Delta^{4,6}$-3 ketones was then calculated by the equation, % $\Delta^{4,7}$-3 ketone = 100 × wt of $\Delta^{4,7}$-3 ketone/wt of $\Delta^{4,7}$-3 ketone + wt of $\Delta^{4,6}$-3 ketone = $100(A_1\epsilon_1 - 100A_2\epsilon_2)/(A_2\epsilon_3 - A_1\epsilon_1 - A_2\epsilon_2)$, where A_1 = log I_0/I of reaction mixture at 239 mμ, A_2 = fog I_0/I of reaction mixture at 284 mμ, ϵ_1 = 26,500 (284 mμ) for **1** and 28,400 (284 mμ) for **3**, ϵ_2 = 3220 (238 mμ) for **1** and 3745 (238 mμ) for **3**, and ϵ_3 = 16,400 (238 mμ) for **7** and 15,600 (238 mμ) for **9**. The ϵ value of $\Delta^{4,7}$-3 ketones **7** or **9** at 285 mμ was only 469 or 440, respectively, and was neglected. In the case of 19-hydroxy-4,6-diene **1**, individual runs with cosolvent mixtures containing 0, 20, 40, 60, 80, or 100% of methanol gave products with 86, 86, 80, 73, 33, and 16% $\Delta^{4,7}$-3-one **7**, respectively. In the case of the 10-methyl analog **3**, runs with cosolvent mixtures containing 0, 20, 40, or 60% methanol gave products with 52, 53, 40, and 1% $\Delta^{4,7}$-3-one **9**, respectively.

When the base treatment in the individual runs was prolonged from 5 to 10 min and also when the isomeric mixtures of 4,6-dienes and 4,7-dienes, *i.e.*, of **1** and **7** or of **3** and **9**, was isolated first by thick layer chromatography on silica gel and was then subjected to uv analysis, essentially the same dependencies of the percentage of $\Delta^{4,7}$-3 ketones **3** and **9** on the percentage of methanol in the respective cosolvent mixtures was observed. When the base treatment was further prolonged, by-products were formed in increasing amounts. No formation of $\Delta^{4,7}$-3 ketones could be observed when the base treatment was carried out in 40 ml of methanol instead of the mixture of cosolvent and dimethyl sulfoxide, and starting materials **1** or **3** were recovered largely unchanged.

Androsta-4,7-diene-3,17-dione (**9**).—When 473 mg of **3** was treated under the conditions outlined above, except that the cosolvent was replaced by dimethyl sulfoxide, a crude product was obtained which, as calculated from its uv spectrum, contained 89% **9**. Chromatography on silica gel yielded a semicrystalline material on elution with benzene–acetone (20:1) which after recrystallization from methanol gave product **9**: mp 129–142°; uv max (EtOH) 238 mμ (ε 15,600); ir ($CHCl_3$) 1736 (17 ketone), 1670 (Δ^4-3 ketone), and 1632 cm^{-1} (>C=C<) nmr 5.82 (s, 1, C-4) and 5.37 ppm (m, 1, C-7).

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.44; H, 8.37.

Registry No.—**2**, 29172-45-0; **7**, 2863-83-4; **8**, 29172-47-2; **9**, 4675-73-4; **10**, 29172-49-4; **11**, 29172-50-7; **13**, 29172-51-8; **15**, 29172-52-9; **16**, 29172-53-0.

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Relative Nucleophilicities of Carbanions Derived from α-Substituted Phenylacetonitriles[1]

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The relative nucleophilicities of carbanions derived from α-substituted phenylacetonitriles toward various alkylating agents have been determined in liquid ammonia solution. The nucleophilicities toward methyl iodide are in the order indicated for sodio derivatives of phenylacetonitrile with the following α substituents: ethyl ~ *n*-butyl > methyl > isopropyl > benzyl > hydrogen > 3-pentyl ≫ phenyl. Other data are presented with isopropyl bromide or *n*-butyl halide as alkylating agent and with potassium or lithium as cation. The results are discussed in terms of inductive and steric effects.

The literature contains many examples of the alkylation of phenylacetonitrile with alkyl halides.[3] Of the many bases and solvents employed, the procedure with sodium amide and liquid ammonia is particularly convenient and efficient but gives a product contaminated with the dialkylation product and unreacted phenylacetonitrile.[4]

Mono- and dialkylation occurs as depicted in Scheme I. Studies of the factors in this reaction which would be important in synthesis have been carried out in this laboratory[5] and elsewhere.[6] We now report a quantitative study of the nucleophilicities in liquid ammonia

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(2) (a) Science Faculty Fellow, National Science Foundation, 1968–1969, on leave from Hampden-Sydney College. (b) National Science Foundation Undergraduate Research Participane. (c) Deceased.

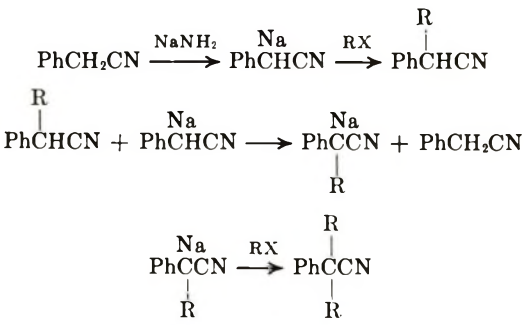
(3) A. C. Cope, H. L. Holms, and H. O. House, *Org. React.*, **11**, 107 (1967).

(4) (a) C. R. Hauser and W. R. Brasen, *J. Amer. Chem. Soc.*, **78**, 494 (1956); (b) W. G. Kenyon, E. M. Kaiser, and C. R. Hauser, *J. Org. Chem.*, **30**, 4135 (1965).

(5) R. L. Bissell, Ph.D. Thesis, Duke University, 1967.

(6) M. Makosza, *Tetrahedron*, **24**, 175 (1968).

SCHEME I

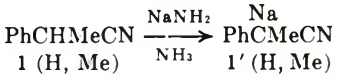


of carbanions derived from α-substituted phenylacetonitriles toward alkyl halides, in which an unusual reactivity series has been found.

In this investigation the *relative* nucleophilicities of such carbanions have been determined by the competitive alkylation of various pairs of carbanions. A quantitative study of relative nucleophilicities by this method must ensure that the initial concentrations of carbanion pairs are accurately known and that the mixtures are homogeneous. The alkylation must be efficient and free of appreciable side reactions. Accurate analyses of alkylation products and residual reactants must be carried out and concentration changes of reactants during alkylation taken into account. All of these conditions have been met in the present study.

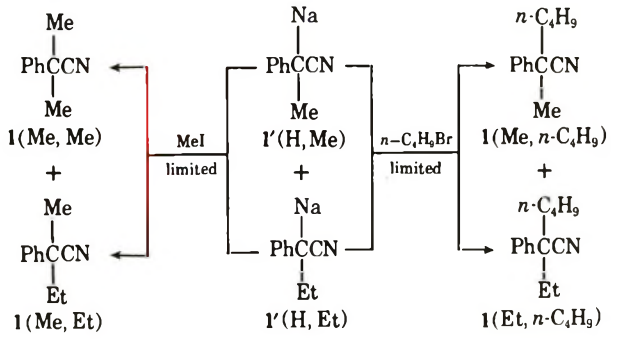
Results

Treatment of an α-substituted phenylacetonitrile **1** with sodium amide in liquid ammonia converts it to the sodionitrile **1′** as shown for the α-methyl derivative. (Throughout this paper a substituted phenylacetonitrile is indicated by the symbol **1** followed by parentheses in which the two α substituents are listed. A prime on **1** designates the derived carbanion.) Relative



nucleophilicities were determined by treating a mixture of two sodionitriles so prepared with a *limited* amount of alkylating agent, to produce alkylation products of the form PhCRR′CN. For example, Scheme II depicts the treatment of an equimolar mixture of **1′** (H, Me) and **1′** (H, Et) with a limited amount of *n*-butyl bromide to produce limited amounts of alkylation products **1** (Me, *n*-C_4H_9) and **1** (Et, *n*-C_4H_9). The more reactive carbanion [**1′** (H, Et) in this case] gave rise to the greater quantity of its alkylation product, and the relative nucleophilicity of the two carbanions toward *n*-butyl bromide was calculated from the alkylation products ratio, as discussed later. Similarly, treatment of the mixture of carbanions with a limited amount of methyl iodide gave a mixture of **1** (Me, Me) and **1** (Me, Et), and the relative nucleophilicity toward methyl iodide was calculated.

SCHEME II



The validity of relative nucleophilicities so determined depends upon the complete conversion of both nitriles to the sodio derivatives before alkylation. While amide ion is clearly a base of sufficient strength to effect the complete conversion,[7] a large excess of amide ion leads to side reactions and a deficiency to very erroneous values for relative nucleophilicities (see Experimental Section). In the present work, the presence of a slight excess of alkali amide in each experiment was ensured by the use of diphenylmethane as an indicator.

Relative nucleophilicities were calculated with the formula in eq 1, in which the parentheses denote con-

$$\text{relative nucleophilicity, nitrile A:nitrile B} = \frac{\left(\begin{matrix}\text{alkylation}\\ \text{product from A}'\end{matrix}\right)}{\left(\begin{matrix}\text{alkylation}\\ \text{product from B}'\end{matrix}\right)} \times \frac{(\text{average B}')}{(\text{average A}')} \quad (1)$$

centrations and the primes indicate the corresponding carbanions. The ratio of concentrations of alkylation products is multiplied by the inverse ratio of average carbanion concentrations during the course of the alkylation, in order to allow for relative concentration changes of the reactant carbanions. The use of the average concentration is considered to be a very good approximation for the effective concentration in this case, inasmuch as carbanion concentration changes were moderate. Final concentrations of starting carbanions were 60–90% of the initial concentrations, and the average concentration was taken to be the mean of the initial and final values. The use of approximate calculations by eq 1 is considered to be more appropriate here than an analytical mathematical treatment, since the value of the first quotient in eq 1 could be determined more accurately than the absolute concentrations of either product (see Experimental Section). The relative nucleophilicities so calculated are concentration adjusted and represent determinations of true relative rates, not limiting values.

Table I records the results of the relative nucleophilicity determinations depicted in Scheme I and of similar experiments using other pairs of carbanions. For a given pair, the initial molar ratio of carbanions was varied from 1 to 3 and that of alkyl halide to total nitrile from 0.12 to 0.45 in various trials. The variations caused no trending in the calculated relative nucleophilicities, giving strong support to the validity of the method. Analyses for total starting material and products were usually 90–100 mol % of the initial totals, indicating that side reactions are unimportant.

The data are internally consistent, as indicated by a comparison of the methylation expt 1, 2, 6, 7, and 8. The relative nucleophilicity value of 1.04 (expt 8)

(7) We estimate the pK of phenylacetonitrile to be about 20 based upon the value of 25 for acetonitrile (see D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 12). The value for ammonia is 34–36 (see D. J. Cram, *ibid.*, pp 14, 20; D. C. Ayers, "Carbanions in Synthesis," Oldbourne Press, London, 1966, p 3).

TABLE I

RELATIVE NUCLEOPHILICITIES OF PAIRS OF α-SUBSTITUTED SODIOPHENYLACETONITRILES, $C_6H_5CNaRCN$ (1′), TOWARD ALKYL HALIDES

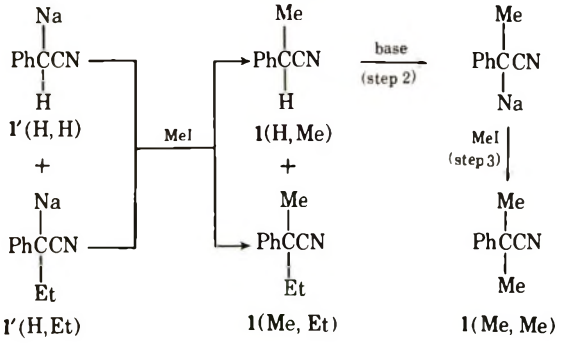
Expt no.	R, in nitrile A	R, in nitrile B	Alkyl halide	Alkylation time, min	Alkylation efficiency,[a] %	No. of trials	Average relative nucleophilicity,[b] A:B
1	Et	H	MeI	10	89–97	4	2.28 ± 0.09
2	n-C_4H_9	H	MeI	10	85–92	3	2.22 ± 0.02
3	$CHMe_2$	H	MeI	10	93–100	3	1.28 ± 0.07
4	$PhCH_2$	H	MeI	10	70–95	3	1.01 ± 0.07
5	$CHEt_2$	H	MeI	10	87–94	2	0.264 ± 0.010
6	Et	Me	MeI	10	65–72	2	1.67 ± 0.06
7	n-C_4H_9	Me	MeI	10	60–71	2	1.64 ± 0.09
8	Et	n-C_4H_9	MeI	10	72–82	2	1.04 ± 0.03
9[c]	$CHEt_2$	Ph	MeI	10	88	1	24.8
10[d]	n-C_4H_9	H	MeI	10	84–86	2	2.70 ± 0.2
11[e]	n-C_4H_9	H	MeI	15	86–87	2	2.42 ± 0.3
12	Et	H	n-C_4H_9Br	20	85–100	3	5.3 ± 0.4
13	Et	H	n-C_4H_9I	10	96–100	2	5.5 ± 0.2
14	Et	H	n-C_4H_9Cl	30–45	20–29	2	4.5 ± 0.1
15	Me	H	n-C_4H_9Br	20	62–70	2	3.2 ± 0.4
16	Et	Me	n-C_4H_9Br	15	82	1	1.57
17	n-C_4H_9	H	Me_2CHBr	30	55–75	2	4.4 ± 0.6
18	$CHEt_2$	H	Me_2CHBr	20–60	10–13	2	0.19 ± 0.04

[a] See Experimental Section. [b] The average deviation is given for each value. [c] Diphenylmethane indicator color was not visible in this case. A 25 mol % excess of $NaNH_2$ was employed. [d] The cation was potassium in this case. [e] The cation was lithium in this case.

for 1′ (H, Et):1′ (H, n-C_4H_9) accords within experimental precision with the value 1.03 for the ratio 1′ (H, Et):1′ (H, H)/1′ (H, n-C_4H_9):1′(H, H) (expt 1, 2) and with the value of 1.02 for the ratio 1′ (H, Et):1′ (H, Me)/1′ (H, n-C_4H_9):1′ (H, Me) (expt 6, 7). Similarly, for n-butylation, the 1′ (H, Et):1′ (H, Me) value of 1.57 (expt 16) accords with the value 1.7 for the ratio 1′ (H, Et):1′ (H, H)/1′ (H, Me):1′ (H, H) (expt 12, 15).

Experiments involving sodiophenylacetonitrile, 1′ (H, H), differed from those involving pairs of α-substituted carbanions in that both mono- and dialkylation products were obtained from 1′ (H, H). Also, in such experiments the alkyl halide employed must not have an alkyl group identical with the α substituent of the other nitrile; otherwise, the monoalkylation product of the latter is identical with the dialkylation product of 1 (H, H). For example, Scheme III illustrates the methylation of a mixture of 1′ (H, H) and 1′ (H, Et).

SCHEME III



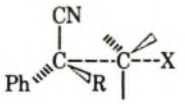
The monoalkylation product 1 (H, Me) is appreciably acidic and underwent ionization as shown by step 2, followed by further reaction with methyl iodide (step 3) to produce 1 (Me, Me). The base involved in step 2 could have been either of the reactant carbanions. A proton transfer reaction of this type would tend to lower the concentration of both carbanions during alkylation to an indeterminant extent; however, the effect would doubtless be greater on the more basic carbanion, probably 1′ (H, Et). The disproportionate lowering of the concentration of 1′ (H, Et) would lead to erroneous values of relative nucleophilicity which would trend toward unity (see eq 1). The lowering would be most pronounced when a relatively large proportion of alkylating agent was taken and when the initial concentration of 1′ (H, H) was large relative to the other carbanion. No trending was observed when such variations of reaction parameters were applied to the given pair of carbanions nor to other similar pairs. It is concluded that the excess amide ion present (see Experimental Section) served as the base in step 2 and that proton transfer reactions among carbanions gave rise to no detectable errors in these experiments. The fact that the second alkylation step (Scheme III, step 3) also consumes alkylating agent has no effect on the validity of the calculations by eq 1, provided the concentration of alkylation products derived from 1′ (H, H) is understood to be the sum of its mono- and dialkylation products.

Discussion

The data of Table I indicate an unusual reactivity series for various 1′ toward methyl iodide. In terms of the α substituents, the nucleophilicities of the sodio derivatives are as follows relative to 1′ (H, H): ethyl, 2.28; n-butyl, 2.22; methyl, 1.37; isopropyl, 1.28; benzyl, 1.01; hydrogen, 1.00; 3-pentyl, 0.26; phenyl, 0.011. Apparently the reaction rate is quite insensitive to the steric bulk of the α substituent. Even with a relatively bulky isopropyl substituent, the carbanion is more reactive than the unsubstituted one. Substitution of the larger 3-pentyl group does decrease the reactivity but not markedly.

The reaction of a carbanion with an alkyl halide is known to proceed by an SN2 mechanism.[3] The very

slight steric effect observed in the present work is ascribed to the fact that the substituent is at the attacking carbanionic center, rather than at the carbon undergoing substitution, and bends away from the alkyl halide as the transition state is approached and the sp^2 hybrid orbitals at the carbanionic center attain more p character. The transition state is depicted by structure 2. The data indicate further that the inductive



2

effects of alkyl groups are comparable to the steric effects in the present cases, if we assume that solvation effects are negligible. Thus, the slightly greater electron-donating effect of ethyl compared to methyl makes 1′ (H, Et) more reactive than 1′ (H, Me) in spite of the larger size of the former (see expt 6). Although models indicate steric hindrance from isopropyl to be somewhat greater than from benzyl, the data show 1′ (H, $CHMe_2$) to be slightly *more* reactive than 1′ (H, $PhCH_2$). Particularly interesting is the benzyl–butyl comparison (expt 2, 4). In view of the previously discussed steric insensitivity of the reaction and the fact that these two groups differ only beyond the first carbon, the lower reactivity of 1′ (H, $PhCH_2$) may be ascribed mostly to inductive effects; the electron-withdrawing effect of the phenyl group partly counteracts the electron-donating effect of the methylene of the benzyl group. Supporting this conclusion is the ethyl–butyl comparison (expt 1, 2). Despite the disparate steric bulk, the carbanion reactivities are nearly equal because of nearly equal inductive effects.

Although the inductive effects of alkyl groups are discussed here in classical electron-donating terms, the results of some recent theoretical calculations indicate that the *more* branched alkyl groups better stabilize adjacent negative charge in the gas phase.[8] However, as pointed out by Lewis,[8a] such stabilization may not occur in solution where solvated ions are involved.

The general steric insensitivity of the reaction is also illustrated by experiments with *n*-butyl and isopropyl halides (Table I). Toward *n*-butyl bromide, 1′ (H, Et) is 1.57 times more reactive than 1′ (H, Me), in agreement with 1.67 for the less bulky alkylating agent methyl iodide. It is interesting that *n*-butyl bromide is more discriminating than methyl iodide, by a factor of about 2, toward the carbanion pair 1′ (H, Et):1′ (H, H) (*cf.* expt 1, 12) as well as the pair 1′ (H, Me):1′ (H, H) (*cf.* expt 1, 6, 15). Despite its greater bulk, *n*-butyl bromide exhibits a stronger preference for the substituted carbanions than does methyl iodide. The identity of the departing halide has little effect upon selectivity for *n*-butylation (expt 12–14), suggesting that the carbon–halogen bond is largely broken in the transition states.

Isopropyl bromide gives about the same discrimination with the 1′ (H, *n*-C_4H_9):1′ (H, H) pair (expt 17) as does *n*-butyl bromide with the 1′ (H, Et):1′ (H, H) pair. Only when a much bulkier substituent, 3-pentyl, is involved, is an overriding steric effect evident. Thus isopropyl bromide gives relatively less reaction with 1′ (H, $CHEt_2$) (expt 18) than does methyl iodide (expt 5).

As expected, the α-phenyl group caused a large decrease in reactivity (expt 9). Both steric and electronic effects deactivate the carbanion in this case. When the data of expt 5 and 9 are compared, 1′ (H, Ph) is about 100 times less reactive than 1′ (H, H) toward methyl iodide.

When the cation was varied among lithium, sodium, and potassium, the pair 1′ (*n*-C_4H_9, H):1′ (H, H) showed approximately the same relative nucleophilicity toward methyl iodide (expt 2, 10, 11). Since the steric requirements of the cations would be expected to be unimportant, it appears that the relative basicity of the carbanionic pair is insensitive to change in alkali metal cation.

Relatively small differences such as those reported here for variations of the α-alkyl group have also been reported in previous studies of structure *vs.* nucleophilicity for ambident[9] carbanions in solvents such as alcohols and ethers. The comprehensive work of Zook and Rellahan[10] on the rates of alkylation of sodium enolates of alkyl phenyl ketones reports, for example, the rates for ethyl bromide with various α-alkyl derivatives of sodioacetophenone. The relative rates are as follows with the indicated α substituents: unsubstituted, 1.0; methyl, 1.6; ethyl, 1.0; *n*-propyl, 0.9; *n*-butyl, 0.8. Thus, it appears that the steric effects, albeit small, are more important in such enolates than in carbanions from phenylacetonitrile. Small alkyl substituent effects have been recorded for other enolates with regard to nucleophilicity[11] and basicity,[12] and for malonic esters[13] and β-keto esters.[14]

Makosza[6] has reported the competitive alkylation of some pairs of α-substituted phenylacetonitriles with alkyl bromides and sodium amide. The product ratios obtained were discussed in terms of their implications for synthesis. No variation of nitrile or bromide proportions was reported and only one case was treated in which both nitriles were substituted. Although no identical carbanion pair–alkyl halide systems were treated in the present work, in comparable cases the product ratios are in qualitative agreement. Relative nucleophilicity calculations cannot be made with Makosza's data since most of the cases report the analysis of only one reactant and its alkylation products, and since only relative product mixture compositions are reported, rather than absolute analyses. While we are in substantial agreement with Makosza's conclusions with regard to synthesis, it should be mentioned that he has employed concentration levels appropriate for synthesis (approximately 40 times more concentrated than

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TABLE II

PREPARATION OF NEW COMPOUNDS

Compd	Registry no.	Method	Yield, %	Bp, °C (mm) or mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
3-Ethyl-2-phenylvaleramide	29850-91-7	A	67	136–136.5[a]	$C_{13}H_{19}NO$	76.05	9.34	6.82	76.04	9.52	6.55
3-Ethyl-2-phenylvaleronitrile	22101-43-5	A	68[b]	111 (2)	$C_{13}H_{17}N$	83.37	9.15	7.48	83.48	9.38	7.30
2-Methyl-2-phenylbutyronitrile	5558-93-0	B[c]	67	70–72 (0.35)	$C_{11}H_{13}N$	82.97	8.23	8.80	82.99	8.24	8.73
2,3-Diphenyl-2-methylpropionitrile	5558-92-9	B[c]	71	165–170 (1)[d]	$C_{16}H_{15}N$	86.84	6.83	6.33	86.99	7.04	6.07
2,3-Dimethyl-2-phenylbutyronitrile	29936-67-2	C[c]	40	84 (1.5)	$C_{12}H_{15}N$	83.19	8.73	8.08	82.94	8.70	8.35
3-Ethyl-2-methyl-2-phenylvaleronitrile	29850-95-1	C[c,e]	66	91–92 (0.7)	$V_{14}H_{19}N$	83.53	9.51	6.96	83.29	9.62	7.08
2-Isopropyl-2-phenylhexanenitrile	29850-96-2	C[e,f]	76	96–96.5 (0.8)	$C_{15}H_{21}N$	83.66	9.83	6.50	83.90	10.09	6.57
3-Ethyl-2-isopropyl-2-phenylvaleronitrile	29850-97-3	C[f]	57[g]	89.5–91 (0.2)	$C_{16}H_{23}N$	83.78	10.11	6.11	83.51	10.26	6.26

[a] Crystallized from benzene. [b] Based on the carboxamide. [c] With MeI. [d] Mp 40.5–42.5° when distillate crystallized. [e] Twice the stoichiometric amounts of $NaNH_2$ and alkyl halide were used. [f] With Me_2CHBr. [g] The crude product contained 20% starting material.

ours) and has not ruled out the possibility of partial solubility.

Experimental Section[15]

Preparation of Mono- and Dialkylphenylacetonitriles.—2-Phenylpropionitrile, 2,3-diphenylpropionitrile, 2-phenylhexanenitrile, and 2-*n*-butyl-2-phenylhexanenitrile were prepared as previously described.[4] Other compounds were prepared by one of the three general methods described below. Reaction mixtures were worked up by neutralizing with 10% HCl, extracting with ether, drying and concentrating the extracts, and distilling or crystallizing the residue. The properties of compounds which appear to be new are given in Table II and those of other compounds in Table III. The starting nitriles used in this work had purity greater than 99.5% by vpc. Dialkylphenylacetonitriles for calibration mixtures had purity greater than 99% by vpc.

Method A.—According to the indirect route of Kaiser and Hauser,[16] α-alkylphenylacetamides were prepared by alkylation of disodiophenylacetamide and dehydrated to the corresponding nitrile with *n*-butyllithium.

Method B.—Monoalkylphenylacetonitriles were alkylated with excess NaH and excess alkyl halide.

Method C.—A monoalkylphenylacetonitrile was stirred 30 min with 4 equiv of $NaNH_2$ in liquid NH_3. Alkyl halide, 4 equiv, was added dropwise over 5–10 min, and the mixture stirred 15–60 min and quenched with NH_4Cl. Dialkylphenylacetonitriles in which the alkyl groups were identical were prepared in one step from phenylacetonitrile by the same procedure.

Relative Nucleophilicity Experiments.—The most critical factor was the quantity of sodium amide taken. Use of less than the stoichiometric amount led to incomplete generation of the more basic (and probably more nucleophilic) carbanion and erroneous alkylation product ratios. While a moderate excess (~20 mol %) of sodium amide did not appear to be harmful, a large excess led to a reduced alkylation efficiency[17] and nonreproducible alkylation product ratios. Accurate determination of the quantity of alkali metal amide taken is difficult experimentally, especially with small quantities. Commercial samples are of questionable purity and generation of the material from the metal *in situ* may be incomplete and subject to side reactions. In the present work the use of diphenylmethane as an indicator served as a rapid, convenient procedure to adjust the concentration of alkali metal amide.

The two nitriles were added to excess alkali metal amide in liquid NH_3 and a small amount (*ca.* 2 mol % of total nitriles) of diphenylmethane was then added to produce the orange diphenylmethide ion. Sodionitrile mixtures made with commercial sodium amide were faintly green and clearly homogeneous. The indicator color was readily visible. When sodium amide generated *in situ* was used, the mixtures obtained were dark colored and opaque, masking the indicator color. Hence a commercial product (Fisher Scientific Co.) was employed for trials with sodium cation. When lithium or potassium amide generated *in situ* was used to form the nitrile carbanions, the indicator color change could be observed satisfactorily. The excess amide ion was neutralized by the addition in small portions of solid NH_4Cl to discharge the orange color (*vide infra*). A moderate amount of sodium amide (10–30 mol % of total nitriles) remains after discharge of the orange color, as shown by control experiments in which an excess of alkyl halide was added to 1′ (H, H). An average of more than one alkyl group per molecule was incorporated [see discussion of dialkylation of 1 (H, H)].

In a typical experiment, 350 ml of anhydrous NH_3 was distilled into a flask equipped with a dewar condenser and mechanical stirrer. The flask was blanketed with N_2, and 50 mmol of commercial $NaNH_2$, weighed under N_2, was introduced into the flask followed by a mixture of two nitriles, totaling *ca.* 12 mmol, in 20 ml of ether.[18] The mixture was stirred for 15 min to give a

(15) Melting points and boiling points are uncorrected. Nmr spectra were determined at 60 MHz on a Varian A-60 spectrometer. Vpc analyses were performed on an F & M Model 700 chromatograph with thermal conductivity detector and mechanical integrator using a 0.25 in. × 20 ft column packed with 20% SE-30 silicone gum rubber. Ethyl ether was distilled from $LiAlH_4$. Alkyl halides were dried and distilled.

(16) E. M. Kaiser and C. R. Hauser, *J. Org. Chem.*, **33**, 3873 (1966).

(17) Alkylation efficiency is used here to mean the fraction of moles of alkylation agent incorporated into nitriles as new alkyl groups.

(18) **1** (H, $PhCH_2$), which is not very soluble in ether, was introduced in solid form.

TABLE III

PREPARATION OF KNOWN COMPOUNDS

Compd	Registry no.	Method	Yield, %	Bp, °C (mm), or mp, °C	Lit. bp, °C (mm), or mp, °C
2-Phenylbutyramide	90-26-6	A	93	73–74	75–77[a]
3-Methyl-2-phenylbutyramide	5470-47-3	A	48	108–110	99–101[b]
2-Phenylbutyronitrile	769-68-6	A	38[c]	102–103 (7)	128 (16)[d]
3-Methyl-2-phenylbutyronitrile	5558-29-2	A	52[c,e]	73–74.5 (0.6)	110 (7)[f]
2-Ethyl-2-phenylhexanenitrile	5558-55-4	B[g]	28	100–105 (0.8)	112–115 (2)[h]
2-Methyl-2-phenylpropionitrile	1195-98-8	C[h]	58[i]	79 (2.5)	100–103 (12)[i]
2,2-Diphenylpropionitrile	5558-67-8	C[k]	60	135 (0.7)	141 (1.5)[l]
2-Isopropyl-3-methyl-2-phenylbutyronitrile	29936-68-3	C[l]	90	93.5 (1.2)	174.4–174.5 (49)[m]
2-Methyl-2-phenylhexanenitrile	4355-47-9	C[n]	56	93–95 (1)	114–115 (4)[h]

[a] N. Bikova and L. Zhelyazkov, *Tr. Nauch.-Issled. Inst. Farm.*, **3**, 29 (1961); *Chem. Abstr.*, **61**, 6948*f* (1964). [b] G. Vasiliu and F. Cocu, *Rev. Chim. (Bucharest)*, **18**, 259 (1967); *Chem. Abstr.*, **67**, 108408m (1967). [c] Based on the carboxamide. [d] D. Zavoianu and F. Cocu, *Rev. Chim. (Bucharest)*, **18**, 2 (1967); *Chem. Abstr.*, **67**, 32438y (1967). [e] Preparation from phenylcyanoacetic acid (ref 13) gave <10% yield. [f] M. Makosza and B. Serafin, *Rocz. Chem.*, **39**, 1401 (1965). [g] With *n*-C_4H_9Br. [h] Mixture of 4 equiv of MeI and 1 equiv of $PhCH_2CN$ added to 4 equiv of $NaNH_2$ in ammonia. [i] Yield 51% by method B. [j] J. F. Bunnett and T. K. Brotherton, *J. Org. Chem.*, **23**, 904 (1958). [k] With MeI. [l] With Me_2CHBr and $PhCH_2CN$. [m] D. J. Cram, F. Elhafez, and H. L. Nyquist, *J. Amer. Chem. Soc.*, **76**, 22 (1954). [n] With *n*-C_4H_9Br using stoichiometric ratio of reactants.

transparent, light green solution. Diphenylmethane, 1–2 drops, was added and a bright orange color appeared at once. Solid NH_4Cl was added in small portions until the orange color was discharged and the green had reappeared. The bright orange color quickly returned and was again discharged in the same manner. The process was repeated four to six times over a period of 20 min until *ca.* 2 mg was sufficient to discharge the orange color and a green or green-orange color persisted for at least 2 min.[19] The alkyl halide in 20 ml of ether was added dropwise with vigorous stirring over a period of 3 min from a dropping funnel blanketed with N_2. The mixture was stirred for the time period indicated in Table I and neutalized with excess NH_4Cl. Ether was added and the NH_3 was allowed to evaporate. The mixture was neutalized with 10% HCl and extracted three times with 100-ml portions of ether. The combined extracts were dried and carefully concentrated *in vacuo* so as not to selectively remove volatile products. To the residue, which contained 50–80% ether, was added the internal standard and the resultant clear solution was analyzed by vpc. A control run without alkylation gave a total nitrile analysis which was 95 mol % of the initial total. An appropriate internal standard was chosen for each experiment to give a vpc peak which fell among the product peaks but was well resolved from them.

All carbanion mixtures were homogeneous. The alkyl halide in ether dissolved immediately upon addition to the NH_3 solution. The rate of mixing of the alkyl halide was faster than the rate of alkylation, even for methyl iodide. If mixing were relatively slow, the product ratio would mirror the ratio of the local concentrations of reactant carbanions.

Vpc Analysis.—Reaction mixtures were chromatographed under isothermal conditions.[20] Every component was eluted. Components were well resolved, with at least a 60% valley between adjacent peaks in the least favorable case. A calibration mixture, with approximately the same composition of nitriles, internal standard, and ether as the reaction mixture, was prepared from pure, authentic compounds and chromatographed immediately following the reaction mixture under identical conditions. Peak areas were related to molar composition by the use of relative response factors,[21] which agreed within 2% relative from day to day. The total analysis of each nitrile with its alkylation products typically exceeded 90 mol % of the initial quantity. A second chromatogram was obtained with a larger sample injection in order to maximize the peak heights of the alkylation products. The calibration mixture was similarly rechromatographed. More precise values of concentrations of alkylation products for eq 1 were obtained from the second chromatogram. Final concentrations of reactant carbanions were obtained from the first chromatogram. Initial carbanion concentrations were calculated from weight data. The average reactant carbanion concentrations for eq 1 were taken to be the mean of the initial and final values.

Nmr Spectra.—Unless otherwise noted, spectra were taken in $CDCl_3$ with respect to internal TMS. All spectra for compounds in Tables II and III accord with assigned structures and are as follows. **3-Ethyl-2-phenylvaleramide**: DMSO-d_6 δ 7.27 (m, 5), 3.42 (d, 1, J = 10.5 Hz, $PhCH_2$), 1.75–1.20 (m, 4, CH_2), 0.90 (t, 3, J = 7 Hz, Me), 0.78 (t, 3, J = 7 Hz, Me). **3-Ethyl-2-phenylvaleronitrile**: δ 7.39 (s, 5), 3.89 (d, 1, J = 5 Hz, PhCH), 1.8–1.1 (m, 5, $CHEt_2$, CH_2Me), 0.93 (t, 6, J = 6 Hz, Me). **2-Methyl-2-phenylbutyronitrile**: CCl_4 δ 7.25 (m, 5), 1.90 (quartet, 2, J = 7 Hz, CH_2), 1.63 (s, 3, PhCMe), 0.93 (t, 3, J = 7 Hz, CH_2Me). **2,3-Diphenyl-2-methylpropionitrile**: CCl_4 δ 7.21 (s, 5), 7.06 (m, 5), 3.00 (s, 2, CH_2), 1.62 (s, 3, Me). **2,3-Dimethyl-2-phenylbutyronitrile**: CCl_4 δ 7.29 (m, 5), 1.95 (m, 1, CH), 1.65 (s, 3, PhCMe), 1.13, 0.82 (d, 3, J = 6.5 Hz, $CHMe_2$). **3-Ethyl-2-methyl-2-phenylvaleronitrile**: δ 7.6–7.1 (m, 5), 1.68 (s, 3, PhCMe), 1.8–0.6 (m, 11, $CHEt_2$). **2-Isopropyl-2-phenylhexanenitrile**: δ 7.33 (s, 5), 2.5–1.7 (m, 3, $CHMe_2$, $CH_2C_3H_7$), 1.19, 0.77 (d, 3, J = 7 Hz, $CHMe_2$). **3-Ethyl-2-isopropyl-2-phenylvaleronitrile**: δ 7.36 (s, 5), 2.53 (septet, 1, J = 7 Hz, Me_2CH), 2.1–1.2 [m, 5, $CH(CH_2Me)_2$], 1.2–0.6 (m, 12, Me_4). **2-Phenylbutyramide**: δ 7.29 (s, 5), 6.1 (m, 2, NH_2), 3.30 (t, 1, J = 7.5 Hz, CH), 1.9 (m, 2, CH_2), 0.86 (t, 3, J = 7.5 Hz, Me). **3-Methyl-2-phenylbutyramide**: δ 7.23 (s, 5), 5.9 (m, 2, NH_2), 2.96 (d, 1, J = 10 Hz, PhCH), *ca.* 2.3 (m, 1, Me_2CH), 1.05, 0.69 (d, 3, J = 6 Hz, Me_2). **2-Phenylbutyronitrile**: CCl_4 δ 7.21 (s, 5), 3.63 (t, 1, J = 7 Hz, CH), 1.85 (m, 2, J = 7 Hz, CH_2), 1.02 (t, 3, J = 7 Hz, Me). **3-Methyl-2-phenylbutyronitrile**: CCl_4 δ 7.30 (s, 5), 3.64 (d, 1, J = 6 Hz, PhCH), 2.02 (m, 1, J = 6.5 Hz, $CHMe_2$), 1.03, 0.99 (d, 3, J = 6.5 Hz, $CHMe_2$). **2-Ethyl-2-phenylhexanenitrile**: δ 7.39 (s, 5), 1.91 (m, 4, J = 7 Hz, CH_2Me and $CH_2C_3H_7$), 1.6–0.5 (m, 10, CH_2Me, $CH_2C_3H_7$). **2,2-Diphenylpropionitrile**: CCl_4 δ 7.23 (s, 10), 2.00 (s, 3, Me). **2-Isopropyl-3-methyl-2-phenylbutyronitrile**: δ 7.33 (s, 5), 2.48 (septet, 2, J = 6.5 Hz, $CHMe_2$), 1.01, 0.87 (d, 3, J = 6.5 Hz, $CHMe_2$).

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(19) The slowness with which the mixture comes to equilibrium probably explains the presence of excess amide ion mentioned previously. With potassium as cation, the color change was fast and permanent. With lithium, the change was very slow and the neutralization process required *ca.* 2 hr.

(20) Mixtures containing components with widely disparate volatilities were chromatographed with a "step" program, in which the initial constant temperature was quickly raised, between components, to a final constant value at which the less volatile components were all eluted.

(21) See S. Dal Nogare and R. S. Juvet, Jr., "Gas–Liquid Chromatography," Interscience, New York, N. Y., 1962, p 197.

Synthesis of *N*,*N*-Bis(2-fluoro-2,2-dinitroethyl)-*N*-alkylamines

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A new reaction for preparing *N*,*N*-bis(2-fluoro-2,2-dinitroethyl)-*N*-alkylamines, which involves the reaction of fluorodinitromethane with *N*,*N*-bis(alkoxymethyl)-*N*-alkylamines, is described. A number of compounds containing different functional groups suitable for further reaction have been prepared. Some initial observations on the scope, limitations, and mechanism are presented.

The Mannich reaction with gem dinitroparaffins[1] was first investigated by Feuer, Bachman, and May[2] and has proved to be a versatile method for the preparation of polynitroalkylamines. However, the literature reports only two examples of the direct synthesis of an *N*,*N*-bis(2,2-dinitroalkyl)-*N*-alkylamine. Bis(2,2-dinitropropyl)glycine[3] was isolated from the reaction of sodium glycinate with 2,2-dinitropropanol in aqueous solution at pH 9.0. Recently, Eremenko and coworkers have reported the preparation of dipotassium tris(2,2-dinitroethyl)amine.[4] While these are the only examples of acyclic tertiary amines of this type, a number of *N*-alkyl-3,3,5,5-tetranitropiperidines have been prepared.[2,5]

Fluorodinitromethane[6] will react with certain carbonium ion precursors containing potential stabilizing groups.[7] During this investigation, it was desired to assess the properties of the amino group in this regard. The compounds which were chosen for reaction were the *N*-substituted *N*,*N*-bis(alkoxymethyl)amines.[8] It was considered that a major advantage, as opposed to the Mannich reaction, would be that the concentration of carbonium ion precursor would be maximum throughout the reaction. A second consideration was that the reaction would be subject to mild acid catalysis.[9] It was thereby hoped that a number of *N*-substituted *N*,*N*-bis(2-fluoro-2,2-dinitroethyl)amines[10] could be prepared which otherwise would be inaccessible.

Results

A first equivalent of fluorodinitromethane reacted readily at ambient temperature with tris(propoxymethyl)amine to form *N*,*N*-bis(propoxymethyl)-2-fluoro-2,2-dinitroethylamine (**1**). A second equivalent of fluorodinitromethane reacted much more slowly to give the bis derivative **2** in 81% yield; a heating

$$(n\text{-PrOCH}_2)_3\text{N} + \text{FC(NO}_2)_2\text{H} \xrightarrow[89\%]{} (n\text{-PrOCH}_2)_2\text{NCH}_2\text{C(NO}_2)_2\text{F} + n\text{-PrOH}$$

1

$$\mathbf{1} + \text{FC(NO}_2)_2\text{H} \longrightarrow [\text{FC(NO}_2)_2\text{CH}_2]_2\text{NCH}_2\text{OR} + [\text{FC(NO}_2)_2\text{CH}_2]_2\text{NH} + \text{ROH}$$

2 **3**

R = Et, *n*-Pr

period of 72 hr at 80° was required to complete the reaction. A by-product obtained in 15% yield was bis(fluorodinitroethyl)amine (**3**). The latter could arise by N-protonation of **2** followed by expulsion of an alkoxymethyl carbonium ion.

$$[\text{FC(NO}_2)_2\text{CH}_2]_2\overset{\text{H}^+}{\text{N}}\text{CH}_2\text{OR} \rightleftharpoons [\text{FC(NO}_2)_2\text{CH}_2]\text{NH} + {}^+\text{CH}_2\text{OR}$$

$${}^+\text{CH}_2\text{OR} + \text{ROH} \longrightarrow \text{CH}_2(\text{OR})_2 + \text{H}^+$$

A third equivalent of fluorodinitromethane did not react to yield the tris amine even under forcing conditions. Apparently fluorodinitromethane is too weakly acidic for catalysis of the last step.[11] Reaction did occur, however, with acetic anhydride–acetic acid to form the acetate **4**.

$$[\text{FC(NO}_2)_2\text{CH}_2]_2\text{NCH}_2\text{OEt} \xrightarrow{\text{AcAn–AcOH}} [\text{FC(NO}_2)_2\text{CH}_2]_2\text{NCH}_2\text{OAc}$$

2 **4**

The expected products were obtained in good to excellent yields from the reactions of fluorodinitromethane with *N*,*N*-bis(ethoxymethyl)-*tert*-butylamine, *N*,*N*-bis(*n*-propoxymethyl)benzylamine, and *N*,*N*-bis(ethoxymethyl)-2-aminoacetaldehyde diethyl acetal.

$$(\text{ROCH}_2)_2\text{NR}_1 + 2\text{FC(NO}_2)_2\text{H} \longrightarrow [\text{FC(NO}_2)_2\text{CH}_2]_2\text{NR}_1 + 2\text{ROH}$$

5, $R_1 = (CH_3)_3C-$

6, $R_1 =$ CH_2-

7, $R_1 = (EtO)_2CHCH_2-$

The *tert*-butyl[12a,b] **5**, benzyl[12c] **6**, and alkoxymethyl derivatives **2** were easily dealkylated with strong acid

(1) A summary of the Mannich reaction through 1962 is included in a review by P. Nobel, Jr., F. G. Borgardt, and W. L. Reese, *Chem. Rev.*, **61**, 19 (1964).

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(3) M. B. Frankel and K. Klager, *ibid.*, **79**, 2953 (1957).

(4) L. T. Eremenko, R. G. Gafurov, and S. I. Sviridov, *Zh. Org. Khim.*, **5**, 31 (1969).

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(6) M. J. Kamlet and H. G. Adolph, *J. Org. Chem.*, **33**, 3073 (1968).

(7) Unpublished data from this laboratory by W. H. Gilligan.

(8) (a) L. H. Bock, U. S. Patent 2,295,709 (Sept 15, 1942). (b) A simple modification of Bock's method was the replacement of hexamethylenetetramine by an appropriate substituted amine.

(9) The pK_a of fluorodinitromethane is 7.70 as determined by T. N. Hall of this laboratory. The same value was reported by V. I. Slovetskii, L. V. Okhobystina, A. A. Fainzil'berg, A. I. Ivanov, L. B. Birynkova, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2063 (1965).

(10) The synthesis of the parent compound bis(fluorodinitroethyl)amine has been reported by H. G. Adolph and M. J. Kamlet, *J. Org. Chem.*, **34**, 45 (1969).

(11) Addition of a strong acid to catalyze trisamine formation is ineffective since the ionization of fluorodinitromethane is thereby depressed.

(12) (a) H. G. Adolph of this laboratory has used the *tert*-butyl group as a protective group during the synthesis of fluorodinitroethylamides. (b) R. N. Lacey, *J. Chem. Soc.*, 1633 (1960). (c) B. Loev, M. A. Haas, and F. Dowals, *Chem. Ind. (London)*, 973 (1968).

to give bis(fluorodinitroethyl)amine (**3**). Overall yields of 85–88% of **3** based on fluorodinitromethane were obtained from the *tert*-butyl derivative.

$$[FC(NO_2)_2CH_2]_2NR \xrightarrow{H^+} [FC(NO_2)_2CH_2]_2NH$$
3

R = $(CH_3)_3C$–, $C_6H_5CH_2$–, $R'OCH_2$–

The formation of ethyl *N,N*-bis(fluorodinitroethyl)-aminoacetate (**8**) required a heating period of 11 days at 80°. A 63% yield of the desired bis amine **8** together

$$(EtOCH_2)_2NCH_2CO_2Et + 2FC(NO_2)_2H \longrightarrow [FC(NO_2)_2CH_2]_2NCH_2CO_2Et + FC(NO_2)_2CH_2NCH_2CO_2Et + FC(NO_2)_2CH_2NCH_2CO_2Et + FC(NO_2)_2CH_2\underset{H}{N}CH_2CO_2Et$$
8 **9** **10**

with 5% of *N,N'*-methylenebis(ethyl *N*-fluorodinitroethylaminoacetate) (**9**) were obtained. The crude reaction mixture also contained an undetermined amount of ethyl *N*-fluorodinitroethylaminoacetate (**10**).[13] **8** hydrolyzed normally to the carboxylic acid **11** under

$$[FC(NO_2)_2CH_2]_2NCH_2CO_2Et \xrightarrow[91\%]{H^+/H_2O} [FC(NO_2)_2CH_2]_2NCH_2CO_2H$$
8 **11**

acidic conditions. The acid **11** was converted into the acyl chloride **12** by treatment with thionyl chloride and, without isolation, was reacted with fluorodinitroethanol[6] to give fluorodinitroethyl *N,N*-bis(fluorodinitroethyl)aminoacetate (**13**).

$$11 \xrightarrow{SOCl_2} [FC(NO_2)_2CH_2]_2NCH_2COCl$$
12

$$12 + FC(NO_2)_2CH_2OH \longrightarrow [FC(NO_2)_2CH_2]_2NCH_2CO_2CH_2C(NO_2)_2F$$
13

In contrast to the results obtained with ethyl *N,N*-bis(ethoxymethyl)aminoacetate, the only product which could be isolated from the reaction of fluorodinitromethane with dimethyl *N,N*-bis(methoxymethyl)-*dl*-aspartate was dimethyl *N*-fluorodinitroethyl-*dl*-aspartate (**14**).[14] The formation of a methylenebis com-

$$(CH_3OCH_2)_2NCH(CH_2CO_2CH_3)CO_2CH_3 \xrightarrow{FC(NO_2)_2H} FC(NO_2)_2CH_2\underset{H}{N}CH(CH_2CO_2CH_3)CO_2CH_3$$
14

pound similar to **9** which might be expected from this reaction is probably precluded because of steric crowding.

The products from *N',N'*-bis(methoxymethyl)-*N*-acethydrazide were the methylenebis compound **15** and *N'*-fluorodinitroethyl-*N*-acethydrazide (**16**) isolated in 52 and 20% yields, respectively.

$$(CH_3OCH_2)_2N\underset{H}{N}COCH_2 \xrightarrow{FC(NO_2)_2H} \text{(15)} + FC(NO_2)_2CH_2NHNHCOCH_3$$
16

15 = $FC(NO_2)_2CH_2\underset{H}{N}COCH_2CH_2CH_2\underset{H}{N}COCH_2CH_2(NO_2)_2F$

Discussion

The first equivalent of fluorodinitromethane reacts rapidly and, within experimental error, quantitatively to give stable isolable compounds with all of the bis-(alkoxymethyl)amines which have been tested.

$$(ROCH_2)_2N{-}R_2 \overset{H^+}{\rightleftharpoons} ROCH_2\overset{R_2}{N}CH_2^+ + ROH$$

$$ROCH_2\overset{R_2}{N}CH_2^+ + FC(NO_2)_2^- \longrightarrow FC(NO_2)_2CH_2\overset{R_2}{N}CH_2OR \quad (1)$$
17

R = Et or *n*-Pr
R_2 = alkyl substituent

A summary of the results collected in Table I strongly indicates that the reaction of a second equivalent of fluorodinitromethane depends on the electronegativity of the attached groups. As the electron-withdrawing

$$17 \overset{H^+}{\rightleftharpoons} FC(NO_2)_2CH_2\overset{R_2}{N}CH_2^+ + ROH \quad (2)$$
18

$$18 + FC(NO_2)_2^- \longrightarrow [FC(NO_2)_2CH_2]_2NR_2$$

R = Et or *n*-Pr
R_2 = substituent

effect increases, side reactions increase to the eventual exclusion of the bis(fluorodinitroethyl)amino compound. These side reactions appear to fall into two main categories: (1) protonation on the amine nitrogen with expulsion of an alkoxymethyl carbonium ion

$$FC(NO_2)_2CH_2\overset{R_2}{N}CH_2OR \overset{H^+}{\rightleftharpoons} [FC(NO_2)_2CH_2\overset{R_2}{\underset{H}{N}}CH_2OR]^+ \longrightarrow FC(NO_2)_2CH_2\underset{H}{N}R_2 + {}^+CH_2OR \quad (3)$$
17

and (2) the formation of a destabilized (energetic) carbonium ion which attacks the mono compound **17**, present in much greater concentration than the fluorodinitromethide ion again followed by the expulsion of an alkoxy carbonium ion.

$$17 \overset{H^+}{\rightleftharpoons} FC(NO_2)_2CH_2\overset{R_2}{N}CH_2^+ \xrightarrow{17} FC(NO_2)_2CH_2\overset{R_2}{N}CH_2\overset{R_2}{N}CH_2(NO_2)_2F + {}^+CH_2OR \quad (4)$$
18 **19**

Reaction 3 will predominate when the carbonium ion **18** is strongly destabilized and steric factors decrease the possibility of the formation of a methylenebis compound. Reaction 4 will tend to predominate when

(13) Identified by tlc and glc comparison of **10** with an authentic sample.
(14) The asparate **14** was purified by chromatography on silica gel and identified by comparison with an authentic sample.

TABLE I

PRODUCT DISTRIBUTIONS FOR THE REACTIONS OF 17 *vs.* σR_2^* VALUES

		% yield of products (R_1 = $FC(NO_2)_2CH_2$–)				Reaction conditions	
R_2	σR_1^* [a]	$(R_1)_2NR_2$	$CH_2(NR_1R_2)_2$	R_1NR_2	$(R_1)_2NH$	Temp, °C	Time, hr
$C(CH_3)_3$	−0.30	90				85	2
$CH_2C_6H_5$	0.22	83				100	2
$CH_2CH(OEt)_2$	0.37[b]	100				80	7
CH_2OEt	0.52[b]	81			15	80	72
CH_2CO_2Et	0.76	63	5	*e*		80	264
$CH(CH_2CO_2CH_3)(CO_2CH_3)$	0.98	0	0	*f*		80	144
$FC(NO_2)_2CH_2$	1.57[c]				68[g]	100	54
CH_3CONH–	1.74[d]	0	52	20		80	24[h]

[a] R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13. [b] Value used is that for CH_3OCH_2. [c] L. A. Kaplan and H. B. Pickard, *J. Org. Chem.*, **35**, 2044 (1970), report a σ^* value of 4.41 for the $FC(NO_2)_2$– groups. A factor of 2.8 was used to determine the value for $FC(NO_2)_2CH_2$. [d] Calculated from σ_I value reported in ref 15b. [e] No attempt was made to isolate the mono compound **10**. [f] After hydrolytic work-up the only products that could be detected by tlc and glc were the monoaspartate **14** and fluorodinitroethanol. [g] The reaction mixture contained 12% of starting material and 4.6% of bis(fluorodinitroethyl)methylamine. [h] Heating the reaction mixture at higher temperatures and sustained periods of time led to decomposition and complex product mixtures.

steric factors are suitable for methylene coupling and when the intermediate carbonium ion **18** is less stable than the alkoxymethyl carbonium ion.

The relationship between the Mannich reaction and those of alkoxymethylamines is obvious and the same influences should be operative in both, though certainly not to the same degree. For the synthesis of bis(2,2-dinitropropyl)glycine[4] and tris(2,2-dinitroethyl)amine,[5] the influence of pH has been emphasized, but it would be perhaps more precise to point to the importance of ionized intermediates for these reactions in stabilizing the respective ions **20** and **21** by decreasing the electronegativity of the attached groups.[15]

$$CH_3C(NO_2)_2CHN(CH_2OH)-CH_2CO_2^- \rightleftharpoons CH_3C(NO_2)_2CH_2N(CH_2^+)-CH_2CO_2^- \quad (5)$$
20

$$[^-C(NO_2)_2CH_2]_2NCH_2OH \rightleftharpoons [^-C(NO_2)_2CH_2]_2NCH_2^+ \quad (6)$$
21

No doubt other 2,2-dinitroalkyl derivatives can be used in place of fluorodinitromethane. The possibility also exists that, by a judicious choice of the 2,2-dinitroalkyl reactants to minimize inductive effects a number of mixed tris(2,2-dinitroalkyl)amines can be prepared. These aspects are now being investigated.

Experimental Section

General (Caution).—The polynitro compounds described in this paper are explosives with undetermined properties and should be handled with due care.

Microanalyses were by Galbraith Laboratories, Knoxville, Tenn. Melting points and boiling points are uncorrected.

Thin Layer Chromatography of Fluorodinitro Compounds.—Extensive use was made of thin layer chromatography to monitor the formation of fluorodinitro compounds. The plates were coated with silica gel G ("Merck"; Brinkmann Instruments, Inc., Westbury, N. Y.) and developed with methylene chloride, benzene, or chloroform.

After drying, the plates were sprayed with a 25% solution of KOH in methanol and dried at 40° for 15 min. The potassium nitrite produced in this step was detected by spraying the plates with an 0.03% solution of diphenylamine in 60% aqueous sulfuric acid. Intense blue spots are formed.

***N,N*-Bis(*n*-propoxymethyl)-2-fluoro-2,2-dinitroethylamine (1).**—To 9.8 g (0.042 mol) of tris(*n*-propoxymethyl)amine, at ice-bath temperature, was added 5.22 g (0.042 mol) of fluorodinitromethane with stirring. The mixture was allowed to come to ambient temperature and let stand for 2 hr. The reaction mixture was then distilled through a short Vigreux column and the fraction boiling at 80–81° (0.02 mm) was collected. The yield was 11.05 g (89%).

Anal. Calcd for $C_{10}H_{20}FN_3O_6$: C, 40.40; H, 6.78; F, 6.39; N, 14.14. Found: C, 40.56; H, 6.81; F, 6.52; N, 14.30.

The nmr spectrum in CCl_4 showed two triplets at δ 0.92 (CH_3) and 3.27 (CH_2O), a multiplet at 1.55 (CH_2), a doublet at 4.07 ($FCCH_2$), and a singlet at 4.19 (NCH_2O).

***N,N*-Bis(2-fluoro-2,2-dinitroethyl)ethoxymethylamine (2).**—A mixture of 3.14 g (0.025 mol) of fluorodinitromethane and 2.39 g (0.0125 mol) of tris(ethoxymethyl)amine was heated at a bath temperature of 80–82° for 72 hr. After cooling and removal of the volatiles *in vacuo*, the residual oil weighing 4.12 g was chromatographed on silica gel (G. Frederick Smith, Columbus, Ohio). The bisethoxymethylamine **2**, 3.48 g (81%), was first eluted with CCl_4–$CHCl_3$ 1:1.

The nmr spectrum in CCl_4 consisted of a quartet at δ 3.34 (OCH_2, J_{HH} = 7 Hz), a triplet at 1.18 (CH_3, J_{HH} = 7 Hz), a doublet at 4.26 ($FCCH_2$, J_{HF} = 17 Hz), and a singlet at 4.10 (NCH_2O). Later eluates contained 0.54 g (15)% of bis(fluorodinitroethyl)amine which was identified by comparison with an authentic sample.

Anal. Calcd for $C_7H_{11}F_2N_5O_9$: C, 24.21; H, 3.19; F, 10.94; N, 20.18. Found: C, 24.28; H, 3.08; F, 11.06; N, 20.30.

***N,N*-Bis(2-fluoro-2,2-dinitroethyl)-*tert*-butylamine (5).**—A mixture of 6.28 g (0.05 mol) of fluorodinitromethane and 4.73 g (0.025 mol) of *N,N*-bis(ethoxymethyl)-*tert*-butylamine was heated at a bath temperature of 85° for 2 hr. After cooling, 7.79 g (90%) of product was obtained by crystallization from ethanol: mp 53–54°; nmr ($CDCl_3$) δ 1.09 s (CH_3, 9 H), 4.15 d (CH_2, J_{HF} = 14 Hz, 4 H).

Anal. Calcd for $C_8H_{13}F_2N_5O_8$: C, 27.83; H, 3.80; F, 11.01; N, 20.29. Found: C, 27.74; H, 3.67; F, 11.24; N, 20.31.

***N,N*-Bis(2-fluoro-2,2-dinitroethyl)benzylamine (6).**—A mixture of 6.28 g (0.050 mol) of fluorodinitromethane and 6.28 g (0.025 mol) of *N,N*-bis(propoxymethyl)benzylamine was heated at 100° for 2 hr. Upon cooling, the product crystallized and was recrystallized from absolute ethanol to give 7.83 g (83%):

(15) (a) Using σ_I values based on ^{19}F shielding effects reported by Taft,[15b] σ^* values of +0.47 and −0.78 can be calculated for the CH_2CO_2Et and the $CH_2CO_2^-$ groups, respectively. A value of +0.7 can be estimated for the CH_2CO_2H group. Using pK_a values for malonic and ethyl malonic acids, σ^* values are calculated to be 0.76 (CH_2CO_2Et), −0.65 ($CH_2CO_2^-$), and +1.05 (CH_2CO_2H). A similar decrease in electronegativity would be expected upon ionization of the dinitroethyl group. (b) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *J. Amer. Chem. Soc.*, **85**, 709 (1963); R. W. Taft and I. C. Lewis, *ibid.*, **80**, 2436 (1958).

mp 77–79°; nmr ($CDCl_3$) δ 7.08–7.41 m (phenyl hydrogens), 4.10 d (NCH_2CF, J_{HF} = 17 Hz), 3.93 s (NCH_2).

Anal. Calcd for $C_{11}H_{11}F_2N_5O_8$: C, 34.83; H, 2.92; F, 10.02; N, 18.47. Found: C, 35.05; H, 3.06; F, 9.90; N, 18.24.

***N,N*-Bis(2-fluoro-2,2-dinitroethyl)aminoacetaldehyde Diethyl Acetal (7).**—A mixture of 6.28 g (0.050 mol) of fluorodinitromethane and 6.23 g (0.025 mol) of *N,N*-bis(ethoxymethyl)aminoacetaldehyde diethyl acetal was heated at a bath temperature of 80° for 7 hr. After cooling, the reaction mixture was taken up in methylene chloride and washed consecutively with 0.33 *N* NaOH and water. After drying with anhydrous magnesium sulfate the solvent was removed *in vacuo* to leave an oil weighing 10.11 g (100%).

The nmr spectrum in CCl_4 showed a multiplet at δ 3.30–3.70 ($COCH_2$, J_{HH} = 7 Hz), two triplets at 4.40 (HCO_2, J_{HH} = 4 Hz) and 1.20 ($OCCH_3$, J_{HH} = 7 Hz), and two doublets at 4.26 ($FCCH_2$, J_{HF} = 17 Hz) and 2.85 (NCH_2C, J_{HH} = 4 Hz). When the multiplet at 3.30–3.70 was irradiated, the triplet at 1.20 collapsed to a singlet. Irradiation of the broadened triplet at 4.40 caused the doublet at 2.85 to collapse to a singlet.

Anal. Calcd for $C_{10}H_{17}F_2N_5O_{10}$: C, 29.64; H, 4.23; F, 9.38; N, 17.27. Found: C, 29.88; H, 4.43; F, 9.57; N, 17.46.

Bis(2-fluoro-2,2-dinitroethyl)amine (3) by Dealkylation of 5.—A solution of 39.45 g (0.114 mol) of **5** in 60 ml of trifluoroacetic acid–methylene chloride 5:1 was allowed to stand at ambient temperature for 18 hr. At this time the solution was clear red and tlc analysis showed only the presence of the bis amine **3**. The solvents were removed *in vacuo* and the residue was recrystallized from CH_2Cl_2–CCl_4 1:1 to yield 30.89 g (95%) of product, mp 44–45°. The identity was confirmed by comparison with an authentic sample.

Ethyl *N,N*-Bis(2-fluoro-2,2-dinitroethyl)aminoacetate (8) and *N,N*-Methylenebis(ethyl *N*-fluorodinitroethylaminoacetate) (9).—A solution of 4.71 g (0.038 mol) of fluorodinitromethane and 4.16 g (0.019 mol) of ethyl *N,N*-bis(ethoxymethyl)aminoacetate in 4 ml of absolute ethanol was heated at a bath temperature of 80° for 11 days, allowed to cool, and stripped of volatiles *in vacuo*.

The residue was dissolved in benzene and chromatographed on silica gel. The fractions were analyzed by tlc. The first material eluted was **8**. After removal of the benzene this was recrystallized from carbon tetrachloride to give 4.33 g (63%): mp 69–70°; nmr ($CDCl_3$) δ 1.30 t (CH_3, J_{HH} = 7 Hz), 3.55 s (NCH_2CO_2), 4.19 d ($FCCH_2$, J_{HF} = 19 Hz), 4.21 q (OCH_2, J_{HH} = 7 Hz).

The methylenebis compound **9** was present in the later eluates and, after removal of the solvent, was recrystallized from carbon tetrachloride to give 0.33 g (5%): mp 85–86°; nmr ($CDCl_3$) δ 1.31 t (CH_3, J_{HH} = 7 Hz), 3.42 s (NCH_2CO_2), 3.89 s (CH_2), 4.09 d ($FCCH_2$, J_{HF} = 19 Hz), 4.33 q (OCH_2, J_{HH} = 7 Hz).

Anal. Calcd for $C_{13}H_{20}F_2N_6O_{12}$: C, 31.84; H, 4.11; F, 7.75; N, 17.14; mol wt, 490.33. Found: C, 32.02; H, 4.35; F, 7.94; N, 16.90; mol wt, 488.

***N,N*-Bis(2-fluoro-2,2-dinitroethyl)aminoacetic Acid (11).**—A solution of 2.55 g (0.007 mol) of **8** in 10 ml of trifluoroacetic acid and 4 ml of 6 *N* hydrochloric acid was refluxed for 8 hr and allowed to cool, and the volatiles were removed *in vacuo*. The solid residue was recrystallized from methylene chloride to yield 2.14 g (91%), mp 140–142°.

The nmr spectrum in CD_3CN showed a singlet at δ 3.56 (NCH_2CO_2) and a doublet at 4.44 ($FCCH_2$, J_{HF} = 18.5 Hz). The H ratio was 2:4. The position of the proton could not be ascertained.

Anal. Calcd for $C_6H_7F_2N_5O_{10}$: C, 20.76; H, 2.03; F, 10.95; N, 20.18. Found: C, 20.65; H, 2.07; F, 11.21; N, 20.14.

2-Fluoro-2,2-dinitroethyl *N,N*-Bis(2-fluoro-2,2-dinitroethyl)aminoacetate (13).—To a solution of 1.0 g (0.003 mol) of *N,N*-bis(fluorodinitroethyl)aminoacetic acid **11** in 5 ml of ethylene chloride was added 0.5 ml of thionyl chloride and a few drops of pyridine. The mixture was gradually heated to 90° and allowed to cool, and the solvent was then removed *in vacuo*. The residue was dissolved in 5 ml of methylene chloride and, after cooling the solution in an ice bath, 0.4 ml of fluorodinitroethanol and 0.3 ml of pyridine were added. The mixture was allowed to warm to ambient temperature and was refluxed for 1 hr. Additional methylene chloride was added, and the solution was washed consecutively with dilute hydrochloric acid, water, and 0.1 *N* sodium hydroxide. After drying with anhydrous magnesium sulfate, the solvents were removed *in vacuo* to give 1.2 g (88%) of a viscous oil: nmr ($CDCl_3$) δ 3.75 s (NCH_2CO_2), 4.22 d ($FCCH_2N$, J_{HF} = 17.5 Hz), 5.28 d ($FCCH_2O$, J_{HF} = 15 Hz). No impurities could be detected by tlc.

Anal. Calcd for $C_8H_8F_3N_7O_{14}$: C, 19.88; H, 1.67; F, 11.80; N, 20.30. Found: C, 20.09; H, 1.63; N, 20.08.

Methylenebis Derivative of *N'*-Fluorodinitroethyl-*N*-acethydrazide (15) and *N'*-Fluorodinitroethyl-*N*-acethydrazide (16).—A solution of 6.28 g (0.05 mol) of fluorodinitromethane in 5 ml of dry ethanol was heated to reflux temperature. Over a period of 2.5 hr, 4.05 g (0.025 mol) of *N',N'*-bis(methoxymethyl)-*N*-acethydrazide in 5 ml of absolute ethanol was added. After refluxing overnight the solution was cooled and the crystalline material which deposited was removed by filtration. After recrystallizing from methanol 2.7 g of **15** (52% based on acethydrazide) was obtained: mp 164–166° dec; nmr (CD_3OD) δ 1.91 s ($COCH_3$), 4.09 s (NCH_2N), 4.42 d ($FCCH_2$, J_{HF} = 17 Hz); nmr (CD_3CN) δ 8.08 s (NHNH).

Anal. Calcd for $C_9H_{14}F_2N_8O_{10}$: C, 25.01; H, 3.26; F, 8.79; N, 25.93; mol wt, 432.28. Found: C, 25.37; H, 3.21; F, 8.91; N, 26.01; mol wt, 430, 433.

The solvent was removed from the above filtrate and the residue was chromatographed on silica gel. By elution with CH_2Cl_2–MeOH 1:1, followed by removal of the solvent and recrystallization of the residue from chloroform, 1.02 g (20%) of **16** was obtained: mp 115–118°; nmr (CD_3OD) δ 1.88 s ($COCH_3$), 4.22 d ($FCCH_2$, J_{HF} = 19 Hz), 4.80 s (CD_3OH).

Anal. Calcd for $C_4H_7FN_4O_5$: C, 22.86; H, 3.36; F, 9.04; N, 26.67. Found: C, 23.03; H, 3.56; F, 8.84; N, 26.61.

Registry No.—**1**, 29925-38-0; **2**, 29925-39-1; **5**, 29925-40-4; **6**, 29925-41-5; **7**, 29853-44-9; **8**, 29925-42-6; **9**, 29925-43-7; **11**, 29925-44-8; **13**, 29925-45-9; **15**, 29925-46-0; **16**, 29925-47-1.

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Isomerization of *N*-Aryl-1-aziridinecarboximidoyl Chlorides to *N*-(2-Chloroalkyl)-*N*-aryl Carbodiimides

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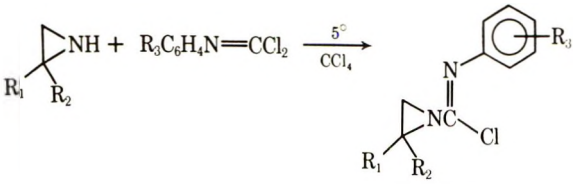
N-Aryl-1-aziridinecarboximidoyl chlorides prepared from aziridines and aryl isocyanide dichlorides undergo facile rearrangement to carbodiimides. The aziridines and carbodiimides were converted to imidazolidinetriones by treatment with oxalyl chloride followed by hydrolysis. The rearrangement to carbodiimides occurs in the neat liquid or in solution and is catalyzed by strong Brønsted acids; kinetic evidence suggests cationic intermediates formed by acid-assisted heterolysis of the C–Cl bond.

Recently we described a novel class of aziridine isomerizations which formally involved a 1,4 shift of X accompanied by the formation of an –N=Y=Z group. These rearrangements were skeletally analogous to the well-known homoallylic rearrangements that have been observed in the cyclopropane series.[1] To date this rearrangement has been utilized to prepare 2-substituted alkyl isothiocyanates,[2] isocyanates,[3,4] and *N*-sulfinylamines.[5] We now wish to report a further

extension of the rearrangement to include the isomerization of *N*-aryl-1-aziridinecarboximidoyl chlorides to *N*-(2-chloroalkyl)-*N*-aryl carbodiimides.

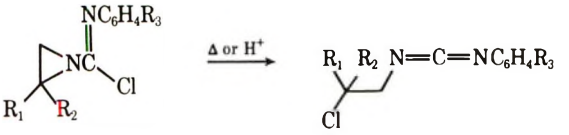
Results

The new class of aziridines, *N*-aryl-1-aziridinecarboximidoyl chlorides, was prepared by allowing equimolar amounts of aziridine to react with the aryl isocyanide dichlorides in the presence of triethylamine.



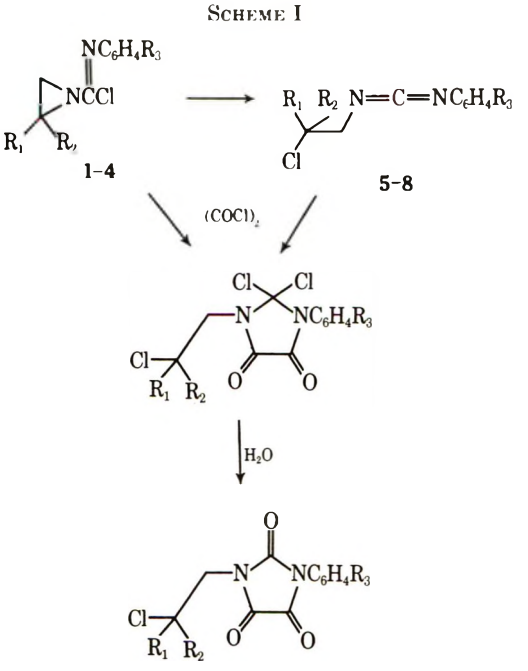
1. $R_1 = R_2 = R_3 = H$
2. $R_1 = R_2 = H$; $R_3 = p$-Cl
3. $R_1 = R_2 = H$; $R_3 = m$-NO_2
4. $R_1 = R_2 = CH_3$; $R_3 = m$-NO_2

It was found that the aziridinecarboximidoyl chlorides could be conveniently isomerized to carbodiimides for preparative experiments at elevated temperatures (*ca.* 40–60°) or at ambient temperatures (25–33°) with an acid catalyst in an aprotic solvent (acetone or acetonitrile). This reaction provided a facile method for preparing unsymmetrical carbodiimides. The acid-catalyzed method appeared to be superior to the thermal procedure since an unidentified polymeric material precipitated from the reaction at higher temperatures. The amount of polymer formation increased with increasing temperatures.



The structures for both the *N*-aryl-1-aziridinecarboximidoyl chlorides and their corresponding rearrangement products, the carbodiimides, were confirmed by infrared and nmr spectroscopy. The nmr data indicated that only one double bond isomer was present, but the configuration was not determined. The conversion of the aziridinecarboximidoyl chlorides and the isomeric carbodiimides to parabanic acids (**9**, **10**, **11**, **12**) has given additional support to the assigned structures. The aziridinecarboximidoyl chlorides or the isomeric carbodimides reacted with oxalyl chloride and yielded dichloroimidazolidinediones which were subsequently converted to the imidazolidinetriones (parabanic acids) when hydrolyzed with water (see Scheme I). The

SCHEME I



1–4 **5–8**

9. $R_1 = R_2 = H$; $R_3 = H$
10. $R_1 = R_2 = H$; $R_3 = Cl$ (*p*)
11. $R_1 = R_2 = H$; $R_3 = NO_2$ (*m*)
12. $R_1 = R_2 = CH_3$; $R_3 = NO_2$ (*m*)

(1) P. De Mayo, "Molecular Rearrangements," Vol. I, Interscience, New York, N. Y., 1964, p 259.
(2) D. A. Tomalia, *J. Heterocycl. Chem.*, **3**, 384 (1966).
(3) D. A. Tomalia and J. N. Paige, *ibid.*, **4**, 178 (1967).
(4) D. A. Tomalia, D. P. Sheetz, and G. E. Ham, *J. Org. Chem.*, **35**, 47 (1970).
(5) D. A. Tomalia, *Tetrahedron Lett.*, 2559 (1967).

reaction of carbodiimides with oxalyl chloride and conversion to parabanic acids is a known reaction.[6]

The rates of isomerization of 1-(*m*-nitrophenyl)-aziridinecarboximidoyl chloride (**3**) to *N*-(2-chloroethyl)-*N*-(*m*-nitrophenyl)carbodiimide (**7**) were monitored by nmr to give data in Tables I and II. Several

Table I

Effect of Solvent Polarity on the Isomerization of 3 at 33°

Solvent	Dielectric constant	Relative rate
DMSO-d_6	47	22,900
Acetonitrile-d_3	37	282
Acetone-d_3	21	199
CH_2Cl_2	9	59
CCl_4	2	1

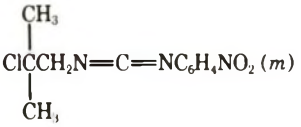
Table II

Acid-Catalyzed Isomerization of 3 to the Carbodiimide 7 in Acetone-d_6 at 33°

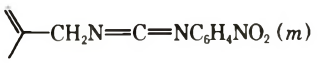
	(Acid)·10^{+3} mol/l.	k_{obsd}·10^{+5} sec^{-1}	$t_{1/2}$ obsd
Perchloric acid catalysis	40.8	430 ± 39	2.7 min
	30	237 ± 14	4.9 min
	20.4	110 ± 8	10.5 min
	12	28 ± 3	41 min
	0	0.9 ± 0.03	27.5 hr
Hydrochloric acid catalysis	26.7	377 ± 18	3.1 min
	21.3	188 ± 10	5.2 min
	16	51 ± 5	22.5 min
	10.65	10 ± 14	117 min
	0	0.9 ± 0.03	27.5 hr

observations indicated that a cationic specie or species were involved as intermediates during the thermal isomerization. It was found that the rate of thermal isomerization (non acid catalyzed) increased with solvent polarity (see Table I). The marked increase with DMSO may be due to solvent participation. It is known that DMSO does react with alkyl halides to form O- or S-alkylated adducts that contain a halide ion.[7,8] It should be noted that the adventitious acid content of the solvents listed in Table I was not known. Hence, these results may not be directly comparable to the acid-catalyzed isomerizations (*vide infra*). The rate of isomerization was retarded by electron-withdrawing groups in the phenyl ring (**1** > **2** > **3**).

In the isomerization of the methyl-substituted aziridinecarboximidoyl chloride (**4**), the presence of two products, **8** and **13** (*ca.* 15%), was indicated by nmr. The



8



13

formation of these compounds could be rationalized by a carbonium ion on the carbon bearing the gem dimethyl group.

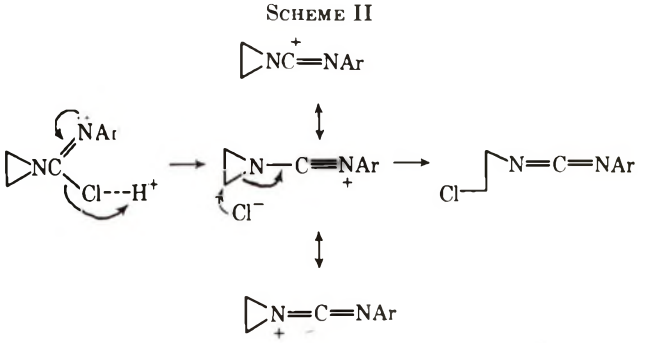
It was observed that the rate of isomerization of **3** to **7** in an aprotic solvent (acetone) was enhanced by addition of catalytic quantities of a strong Brønsted acid. The rates of these acid-catalyzed isomerizations were observed using hydrochloric and perchloric acids as catalysts. The results from these rate studies are summarized in Table I.

Addition of chloride ion (from tetramethylammonium chloride) did not catalyze the isomerization of **3** to **7** in acetone-d_6 at 33°. The rate of isomerization was 2.2×10^{-5} sec^{-1}; the small increase of this compared to the rate in pure acetone-d_6 (0.9×10^{-5} sec^{-1}) was ascribed to a salt effect since the rate of isomerization of **3** to **7** was found to be 1.8×10^{-5} sec^{-1} when tetramethylammonium fluoroborate was added instead of the chloride salt (the concentration of both quaternary salts was 0.03 *M*). It was interesting to observe that isomerization of **3** to **7** in acetone-d_6 appeared to be catalyzed by the addition of lithium chloride ($k = 8 \pm 0.7 \times 10^{-5}$ sec^{-1}, acetone d_6 saturated with lithium chloride). The small lithium ion probably acted as a catalyst for the isomerization in a manner similar to the proton. However, an unusual salt effect has not been eliminated as a possible explanation for the apparent lithium chloride catalysis.

The effect of acid upon the isomerization of **3** to carbodiimide **7** was not completely understandable, and, thus, one can only speculate on the role of the catalyst. The acid-catalyzed nature of the reaction was very apparent (see Table II). However, the order of the acid dependence and the variables (*e.g.*, the effect of increased electrolyte on the activity of the protonic species and chloride ion) created by addition of acid to the reaction were not determined.

One interpretation of the data would require the acid catalyst to assist the cleavage of the carbon–chlorine bond. An alkylated nitrilium salt (or one of its resonance forms) would be the resultant intermediate. The nitrilium salt could be transformed to a carbodiimide when attacked by chloride ion. This reaction pathway is shown in Scheme II. Bartlett

Scheme II



and Pöckels interpreted the autocatalysis of the camphene hydrochloride solvolysis as an acid solvation of a leaving chloride ion.[9] Thus, utilization of the acid catalyst for the solvation of the leaving chloride ion seemed justified. Furthermore, the weakness of the carbon–chlorine bond in aziridine **3** was demonstrated when a dichloromethane solution of **3** was allowed to react with silver tetrafluorobroate. An exothermic reaction ensued and a precipitate of silver chloride was observed immediately.

The acid catalyst did, however, not appear to be acting in the "classical" sense for acid-catalyzed

(6) H. Ulrich and A. A. R. Sayigh, *J. Org. Chem.*, **30**, 2781 (1965).
(7) S. G. Smith and S. Winstein, *Tetrahedron*, **3**, 317 (1958).
(8) R. Kuhn and H. Trischmann, *Justus Liebigs Ann. Chem.*, **611**, 117 (1958).
(9) P. D. Bartlett and I. Pöckels, *J. Amer. Chem. Soc.*, **60**, 1585 (1938).

aziridine ring ruptures (*i.e.*, protonation of the aziridinyl nitrogen atom followed by ring cleavage). If protonation is indeed a step in the course of isomerization of these aziridines to carbodiimides, resonance arguments for the delocalization of the ensuing positive charge can be invoked to explain why protonation should occur on the imidoyl nitrogen rather than on the aziridinyl nitrogen atom. Furthermore, it has been demonstrated that electrophillic attack on (1-aziridinyl)-2-oxazolines, a system very analogous to these aziridineimidoyl chlorides, occurs exclusively at the nitrogen atom β to the aziridine ring.[10]

Experimental Section

Nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60 spectrometer. Chemical shifts are reported as parts per million (δ) relative to tetramethylsilane. The ambient temperature of the probe of the Varian A-60 spectrometer was maintained at 33° by a large volume (40 gal) of recirculating, deionized, cooling water. The cooling water was maintained at constant temperature with a refrigeration apparatus. The temperature of the probe was determined by the shift of the signal for the hydroxyl and methyl protons of methanol.[11] Infrared spectra were recorded on a Beckman IR-5 spectrometer. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Deuterated solvents were purchased from Stohler Isotope Chemicals.

The *p*-chlorophenylisocyanide dichloride was purchased from Eastman Organic Chemicals. Phenylisocyanide dichloride and 3-nitrophenylisocyanide dichloride were prepared by reaction of formanilide and 3-nitroformanilide (K & K Laboratories) with thionyl chloride and sulfuryl chloride, respectively.[12]

***N*-Aryl-1-aziridinecarboximidoyl Chlorides (1–3).**—While stirring a solution of aryl isocyanide dichloride (0.1 mol) in 75 ml of carbon tetrachloride at 0–5°, a solution of aziridine (0.1 mol, Dow Chemical Co.) and triethylamine (0.1 mol) in 75 ml of carbon tetrachloride was added dropwise over a period of 1.5 hr. The reaction temperature was maintained below 5° during addition by external cooling with ice. (Reaction leading to **3** was very exothermic.) The mixture stirred for 1–2 hr at room temperature; then triethylamine hydrochloride was removed from the reaction by filtration. The aziridines **1**, **2**, and **3** were isolated from these filtrates by removal of solvent with a vacuum as room temperature. Compound **1** was isolated as a light yellow, thermolabile oil; compounds **2** and **3** were obtained as crystalline solids, mp 23–25° (from hexane with Dry Ice cooling) and 68–70° (from diethyl ether, Dry Ice cooling), respectively. Both **2** and **3** could be stored in a freezer (−5 to 0°) for several months without appreciable decomposition. In one instance a neat sample of compound **2** polymerized exothermally to an intractable mass containing carbodiimide while being stored in a refrigerator. Yields of *N*-aryl-1-aziridinecarboximidoyl chlorides varied between 88 and 100%.

Spectral and analytical data for these compounds are as described below.

1: Infrared spectrum 1950 cm^{-1} (N=C); nmr spectrum (CCl_4) δ 2.36 (4 H, singlet, aziridine protons), 7.52–6.62 (5 H, complex multiplet, aromatic protons). It (**1**) was too unstable to purify for combustion analyses.

2: Infrared spectrum 1660 cm^{-1} (N=C); nmr spectrum (CCl_4) δ 2.40 (4 H, s, aziridine protons), 7.22 (2 H, d, aromatic protons), 6.72 (2 H, d, aromatic protons).

Anal. Calcd for $C_9H_8Cl_2N_2$: C, 50.3; H, 3.72; N, 13.0. Found: C, 50.2; H, 3.57; N, 13.07.

3: Infrared spectrum 1650 cm^{-1} (N=C); nmr spectrum (CCl_4) δ 2.51 (4 H, s, aziridine protons), 7.02–8.09 (4 H, multiplet, aromatic protons).

Anal. Calcd for $C_9H_8ClN_3O_2$: C, 48.0; H, 3.55; N, 18.7. Found: C, 48.3; H, 3.57; N, 18.5.

***N*-(*m*-Nitrophenyl-1-(2,2-dimethylaziridine)carboximidoyl Chloride (4).**—According to the above procedure, a solution of 2,2-dimethylaziridine (0.1 mol, Dow Chemical Co.) and triethylamine (0.1 mol) in 75 ml of carbon tetrachloride was added to a solution of 3-nitrophenyl isocyanide dichloride (0.1 mol) also in 75 ml of carbon tetrachloride. After removing triethylamine hydrochloride and solvent in the usual manner, a low melting, white crystalline product precipitated from the carbon tetrachloride filtrate upon storing in a freezer (−20°) overnight. This compound was identified as *N*-(*m*-nitrophenyl)-1-(2,2-dimethylaziridine)carboximidoyl chloride (**4**): mp 26–28° (with an exotherm and spontaneous isomerization to carbodiimide); infrared spectrum (CCl_4) 1650 cm^{-1} (N=C); nmr spectrum (CCl_4) δ 1.44 [6 H, s, $C(CH_3)_2$], 2.42 (2 H, s, CH_2), 7.0–8.06 (4 H, multiplet, aromatic protons).

Anal. Calcd for $C_{11}H_{12}ClN_3O_2$: C, 52.1; H, 4.73; N, 16.5. Found: C, 52.1; H, 4.76; N, 16.3.

Rate Determinations.—The rates of isomerization of **3** in various solvents was accomplished by first weighing a sample (40 mg) of **3** into an nmr tube. Dibenzyl ether (35 μl) and the solvent (250 μl) in question were added to the nmr tube. The integral of the aziridinyl protons at δ 2.51 was compared to the methylene protons of dibenzyl ether at δ 4.55 with respect to time. The tube was placed in a constant temperature bath set at 33° and periodically removed to record the relative integrals of the two signals. The following results were obtained: solvent ($k \times 10^5$ sec^{-1}), DMSO (100 ± 0.1), acetonitrile-d_3 (1.23 ± 0.05), acetone-d_6 (0.9 ± 0.03), CH_2Cl_2 (0.251 ± 0101), CCl_4 (0.00437 ± 0.0006).

A stock solution of perchloric acid in acetone-d_6 was prepared for the perchloric acid catalyzed isomerizations of **3** in acetone-d_6 at 33°. The solution was made by diluting 60 × 10^{-6} l. (60 μl) of 5.71 *N* perchloric acid to 1.0 ml with acetone-d_6. A sample (40 mg) of compound **3** was weighed into an nmr tube. Dibenzyl ether (35 μl) and acetone-d_6 (250 μl − *X*; *X* = microliters of stock perchloric acid–acetone-d_6 solution) were added at time zero. The integral of the azirdinyl protons at δ 2.51 was compared to the methylene protons of dibenzyl ether at δ 4.55. A known volume of the stock perchloric acid–acetone-d_6 solution was added to the nmr tube, the tube was quickly inverted, and a timer was activated. The integral of the two signals at δ 2.51 and 4.55 were monitored with respect to time. The results are recorded in Table II.

A stock solution of hydrochloric acid was prepared for the hydrochloric acid catalyzed isomerization of **3** in acetone at 33°. The solution was made by diluting 30 × 10^{-6} l. (30 μl) of 11.6 *N* hydrochloric acid to 1.0 ml with acetone-d_6. A sample of **3** (40 mg) was weighed into an nmr tube. Benzyl benzoate (70 μl) and acetone-d_6 (240 μl − *X*; *X* = microliters of stock hydrochloric acid-acetone-d_6 solution) were added at time zero. Also sufficient deuterium oxide was added to the reaction solution in addition to the H_2O introduced with the hydrochloric acid stock solution such that the total amount of "water" present was 3.6 × 10^{-4} mol. The integral of the aziridinyl protons at δ 2.51 was compared to the methylene protons of benzyl benzoate at δ 5.34. Then a known volume of the stock hydrochloric acid–acetone-d_6 solution was added to the nmr tube, the tube was quickly inverted, and a timer was activated. The integral of the two signals at δ 2.51 and 5.34 were monitored with respect to time. The results are recorded in Table II.

The rate coefficients, k_{obsd}, where reckoned as −2.30 times the slopes of plots of log (1 − C_d) against time. The slopes were determined by a least-squares treatment of the data, and the errors reported in the rate coefficients were the standard deviations of the slopes. The conversion fraction, 1 − C_d, was defined as the amount of aziridine compound **3** present at time = *t* divided by the amount of aziridine compound **3** at time = zero (beginning of reaction). The quantity, 1 − C_d, was experimentally obtained from the quotient: the millimeters of integration for the aziridinyl protons at time = *t* divided by the millimeters of integration for the aziridinyl protons at time = zero. Integrations were normalized with respect to the millimeters of integration for the internal standard at time = *t* with the median millimeters of integration obtained for the internal standard during the course of a kinetic run. Kinetic runs were generally followed to 70–80% completion, but the slopes were usually obtained by plotting the first 50% of the isomerization since the quantity 1 − C_d became increasingly difficult to determine accurately.

Isomerization of 1 to Carbodiimide 5.—A sample of **1** (4 g)

(10) D. A. Tomalia, N. D. Ojho, and B. P. Thill, *J. Org. Chem.*, **34**, 1400 (1969).

(11) Varian Analytical Instrument Division, Palo Alto, Calif., Publication 87-202-006, pp 4–12.

(12) E. Kuhle, *Angew. Chem.*, **74**, 861 (1962).

was dissolved in carbon tetrachloride (20 ml) and heated in a constant temperature bath at 40°. The conversion from **1** to **5** could be monitored by nmr spectroscopy. After heating for 14 hr the signal for the aziridine protons at δ 2.40 had disappeared. The carbon tetrachloride was removed under reduced pressure to yield a water-white liquid identified as carbodiimide **5**: infrared spectrum 2140 cm^{-1} (N=C=N); nmr spectrum (CCl_4) δ 3.62 (4 H, s, $ClCH_2CH_2N$=), 6.6–7.5 (5 H, m, aromatic protons).

The 1-(2-chloroethyl)-3-phenyl-2,2-dichloroimidazolidine-4,5-dione can be prepared by the reaction of either carbodiimide **5** or aziridine **1** with oxalyl chloride. A sample (4 g, 0.0221 mol) of either carbodiimide **5** or aziridine **1** was dissolved in carbon tetrachloride (16 ml). The carbon tetrachloride solution was added to a solution of oxalyl chloride (4.3 g, 0.033 mol, Eastman Organic Chemicals) in dichloromethane (30 ml) over a period of 10 min. The reaction solution was then heated at 43–45° for 1 hr. The solvent was removed under reduced pressure and a light yellow solid (6.25 g, 92%) was obtained whose spectral data were consistent with 1-(2-chloroethyl)-3-phenyl-2,2-dichloroimidazolidine-4,5-dione: infrared spectrum (Fluorolube) 1766 cm^{-1} (carbonyl); nmr spectrum (acetonitrile-d_3) δ 7.6 (5 H, s, aromatic protons), 4.4–3.7 (4 H, m, $ClCH_2CH_2N$). Ulrich and Sayigh reported a carbonyl absorption of 1766 cm^{-1} for 1,3-dicyclohexyl-2,2-dichloroimidazolidine-4,5-dione.[6]

1-(2-Chloroethyl)-3-phenylimidazolidine-2,4,5-trione (9).—A sample (5.7 g) of the crude 1-(2-chloroethyl)-3-phenyl-2,2-dichloroimidazolidine-4,5-dione was mixed with water (100 ml) and allowed to sit at room temperature for 18 hr. The crystalline product (4.1 g, 88%) was collected by vacuum filtration. The product was recrystallized from dichloromethane–ether to yield a material identified as 1-(2-chloroethyl)-3-phenylimidazolidine-2,4,5-trione (**9**): mp 110–112°; infrared spectrum 1735 cm^{-1} (carbonyl); nmr spectrum (acetonitrile-d_3) δ 7.6–7.2 (5 H, m, aromatic protons), 4.2–3.6 (4 H, 9-line multiplet, spacing = 4 Hz, $ClCH_2CH_2N$).

Anal. Calcd for $C_{11}H_9N_2O_3Cl$: C, 52.3; H, 3.59; N, 11.1. Found: C, 51.9; H, 3.69; N, 11.1.

Isomerization of 2 to Carbodiimide 6.—A sample of **2** (0.04 g) was dissolved in carbon tetrachloride (0.3 ml) and heated in a water bath at 40°. The conversion from **2** to **6** could be monitored by nmr spectroscopy. After being heated for 31 hr the signal for the aziridine protons at δ 2.36 had completely disappeared. Evaporation of the carbon tetrachloride yielded a liquid which was identified as carbodiimide **6**: infrared spectrum 2130 cm^{-1} (N=C=N); nmr spectrum (CCl_4) δ 6.8–7.4 (4 H, m, aromatic protons), 3.7 (4 H, s, $ClCH_2CH_2N$=).

The 1-(2-chloroethyl)-3-(*p*-chlorophenyl)-2,2-dichloroimidazolidine-4,5-dione can be prepared by the reaction of either aziridine (**2**) or carbodiimide (**6**) with oxalyl chloride. A sample (1.96 g, 0.0091 mol) of either **2** or carbodiimide **6** was dissolved in dichloromethane (10 ml). This solution was added dropwise to a solution of oxalyl chloride (1.73 g, 0.0136 mol, Eastman Organic Chemicals) in dichloromethane (40 ml) over a period of 10 min. When the addition was complete the reaction was refluxed for 45 min. The dichloromethane was removed under a reduced pressure to yield a crude material (2.7 g, 87%, mp 125–35°) whose spectral data were consistent with 1-(2-chloroethyl)-3-(*p*-chlorophenyl)-2,2-dichloroimidazolidine-4,5-dione: infrared spectrum (Fluorolube) 1765 and 1750 cm^{-1} (carbonyl); nmr spectrum (acetonitrile-d_3) δ 3.8–4.3 (4 H, m, $ClCH_2CH_2N$), 7.6–7.0 (4 H, m, aromatic protons).

1-(2-Chloroethyl)-3-(*p*-chlorophenyl)imidazolidine-2,4,5-trione (10).—A sample (2.5 g) of the crude 1-(2-chloroethyl)-3-(*p*-chlorophenyl)-2,2-dichloroimidazolidine was stirred with water (75 ml) for 3 hr. The product was collected by vacuum filtration and allowed to dry at room temperature overnight to yield 2 g (95%). After recrystallization from dichloromethane–ether this material was identified as 1-(2-chloroethyl)-3-(*p*-chlorophenyl)imidazolidine-2,4,5-trione: mp 137–138°; infrared spectrum (Fluorolube) 1730 cm^{-1} (carbonyl); nmr spectrum (acetonitrile-d_3) δ 7.2–7.8 (4 H, m, aromatic protons), 3.6–4.2 (4 H, 6-line multiplet, spacing = 5–4–4–4–5 Hz, $ClCH_2CH_2N$).

Anal. Calcd for $C_{11}H_8N_2O_3Cl_2$: C, 46.02; H, 2.89; N, 9.77. Found: C, 46.07; H, 2.92; N, 9.78.

Isomerization of 3 to Carbodiimide 7.—A sample (0.3 g, 1.33 mmol) of **3** was placed in a tube fitted with a condenser and drying tube. The tube was heated in a water bath at 68° for 12 min. The resultant yellow liquid (0.3 g, 100%) was identified as carbodiimide **7**: infrared spectrum 2145 cm^{-1} (N=C=N); nmr spectrum (CCl_4) δ 3.82 (4 H, s, $ClCH_2CH_2N$=), 7.4–8.1 (4 H, m, aromatic protons).

Anal. Calcd for $C_9H_8ClN_3O_2$: C, 48.0; H, 3.55. Found: C, 48.5; H, 3.53.

1-(2-Chloroethyl)-3-(*m*-nitrophenyl)imidazolidine-2,4,5-trione (11).—The 1-(2-chloroethyl)-3-(*m*-nitrophenyl)-2,2-dichloroimidazolidine-4,5-dione can be prepared by the reaction of either aziridine **3** or carbodiimide **7** with oxalyl chloride. A sample (0.5 g, 2.22 mmol) of either carbodiimide **3** or aziridine **7** was taken up in dichloromethane and added portionwise to a stirred solution of oxalyl chloride (0.423 g, 3.33 mmol, Eastman Organic Chemicals) in 8 ml of dichloromethane over a period of 10 min. The reaction was very exothermic. After being refluxed for 30 min, the solvent was removed under reduced pressure to yield a white, crystalline residue (0.95 g, 96%) and melted at 147–150°. Spectral data were consistent with the proposed product, 1-(2-chloroethyl)-3-(*m*-nitrophenyl)-2,2-dichloroimidazolidine-4,5-dione: infrared spectrum (Fluorolube) 1766 cm^{-1} (carbonyl).

The above crude product (0.75 g) was allowed to stir with water (25 ml) at room temperature for several hours. A white crystalline product was collected by filtration and washed with four 10-ml portions of cold water. The aqueous filtrate was very acidic (pH ≅ 1). The air-dried crude product melted at 116–119° (0.4 g, 63%). Three recrystallizations from dichloromethane–ether gave a material identified as 1-(2-chloroethyl)-3-(*m*-nitrophenyl)imidazolidine-2,4,5-trione (**11**): mp 117–119°; infrared spectrum (Fluorolube) 1724 and 1742 cm^{-1} (carbonyl); nmr spectrum (acetonitrile-d_3) δ 7.6–8.4 (4 H, m, aromatic protons), 3.96 (4 H, 8-line multiplet, spacing = 3–4–4–4–4–4–3 Hz, $ClCH_2CH_2N$).

Anal. Calcd for $C_{11}H_8ClN_3O_5$: C, 44.4; H, 2.69; N, 14.1. Found: C, 44.0; H, 2.72; N, 14.3.

Isomerization of 4 to Carbodiimide 8.—A sample of **4** (0.3 g) was placed in a test tube equipped with a thermocouple. Upon warming to 28°, the white crystals melted and an exothermic reaction began. Temperature rose to 44°. This melt was analyzed by nmr and infrared spectroscopy and found to be completely converted to the carbodiimide. The infrared spectrum showed that the band at 1660 cm^{-1} (N=C) had disappeared, whereas an intense band at 2130 cm^{-1} (N=C=N) had appeared. Characteristic nmr signals (CCl_4) for the aziridine ring in **4** were absent. New resonance bands were present at δ 1.78 (6 H, singlet), 3.65 (2 H, singlet), and two complex multiplets centered at 7.94 and 7.42 (4 H). These were assigned to CH_3C-CH_3, CH_2, and the aromatic ring, respectively, in *N*-(2-chloro-2-methylpropyl)-*N*-*m*-nitrophenylcarbodiimide (**8**). Two broadened singlets at δ 1.85 (CH_3) and 4.01 (CH_2), as well as a finely split multiplet at δ 5.02 were assigned to a small amount of *N*-methylallyl-*N*-*m*-nitrophenylcarbodiimide (**13**). Both methyl and methylene group integrations indicated that about 15–18 mol % of unsaturated carbodiimide was present in this melt.

1-(2-Chloro-2-methylpropyl)-3-(*m*-nitrophenyl)imidazolidine-2,4,5-trione (12).—A dichloromethane solution (10 ml) of crude **8** (3.3 g) was added dropwise to a solution of oxalyl chloride (2.48 g, 0.0195 mol, Matheson Coleman and Bell) in dichloromethane (20 ml) over a period of 10 min. The reaction solution was allowed to reflux for 30 min after the addition was complete. The dichloromethane was removed under reduced pressure and 1-(2-chloro-2-methylpropyl)-3-(*m*-nitrophenyl)-2,2-dichloroimidazolidine-4,5-dione, a light tan crystalline material, was isolated (4.25 g, 82%): mp 154–167°; infrared spectrum (Fluorolube) 1760 cm^{-1} (carbonyl). Crude dichloroimidazolidine-4,5-dione (4.1 g) was stirred with water (75 ml) for 2 hr and a product (3.3 g, 98%) was collected by vacuum filtration. The product was recrystallized from dichloromethane–ether and was identified as 1-(2-chloro-2-methylpropyl)-3-(*m*-nitrophenyl)imidazolidine-2,4,5-trione (**12**): mp 183–185°; infrared spectrum (Fluorolube) 1735 cm^{-1} (carbonyl); nmr spectrum (acetonitrile-d_3) δ 7.6–8.4 (4 H, m, aromatic protons), 3.99 (2 H, s, $ClCH_2C$), 1.65 [6 H, s, $C(CH_3)_2$].

Anal. Calcd for $C_{13}H_{12}N_3O_5Cl$: C, 47.8; H, 3.95; N, 12.9. Found: C, 47.6; H, 3.83; N, 13.0.

Registry No.—**1**, 29494-60-8; **2**, 29494-61-9; **3**, 29494-62-0; **4**, 29576-45-2; **5**, 29494-63-1; **6**, 29494-64-2; **7**, 29494-65-3; **8**, 29494-66-4; **9**, 29494-67-5;

10, 29478-09-9; **11**, 29478-10-2; **12**, 29478-11-3; 1-(2-chloroethyl)-3-phenyl-2,2-dichloroimidazolidine-4,5-dione, 29478-12-4; 1-(2-chloroethyl)-3-(*p*-chlorophenyl)-2,2-dichloroimidazolidine-4,5-dione, 29576-46-3; 1-(2-chloroethyl)-3-(*m*-nitrophenyl)-2,2-dichloroimidazoline-4,5-dione, 29478-13-5; 1-(2-chloro-2-methylpropyl)-3-(*m*-nitrophenyl)-2,2-dichloroimidazolidine-4,5-dione, 29641-82-5.

Chlorination of Oximes. I. Reaction and Mechanism of the Chlorination of Oximes in Commercial Chloroform and Methylene Chloride

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The chlorination of benzaldoximes in commercial chloroform and methylene chloride was undertaken. It was found that substituted oximes which possess electron-wtihdrawing groups gave benzal chloride derivatives upon chlorination in methylene chloride and pure chloroform. On the other hand, benzhydroxamic chloride derivatives were obtained when chlorination was performed in commercial chloroform and methylene chloride containing 0.75% ethanol. In the presence of an electron-donating group, a mixture of benzal chloride and benzhydroxamic chloride derivatives was isolated irrespective of the solvent used. Benzhydroxamic chloride (I) was the sole product when chlorination was catalyzed by triethylamine. It appears that triethylamine and ethanol catalyzed the benzhydroxamic chloride formation. The abnormal chlorination reaction of benzaldoxime, *o*-hydroxybenzaldoxime (XI), and *p*-dimethylaminobenzaldoxime (XVII) in methylene chloride solution is particularly interesting. The mechanism of benzal chloride formation in the chlorination of oximes was examined. It is assumed that *p*-nitro-α-nitrosobenzyl chloride (XXa) emerged in the course of reaction; this was demonstrated by chemical evidence and spectroscopic studies. Two reaction mechanisms are proposed for the formation of benzal chloride. In the first of the mechanisms it is suggested that the chloronitroso intermediate decomposed unimolecularly to give a carbanion and a nitrosyl ion. In the second one, it can be considered as a nucleophilic displacement on the nitroso group, perhaps by chloride ion, and that the carbanion and nitrosyl chloride are thereby produced. The mechanism of isomerization of aromatic α-chloro-α-nitroso compounds was proposed according to the experimental results. Generally, it is assumed that the isomerization process could be separated into three categories. (1) One way is amine-catalyzed isomerization through a carbanion intermediate. (2) Ethanol-catalyzed isomerization gave a cyclic intermediate through intermolecular H bonding with electron-withdrawing substituted α-chloro-α-nitroso compound. (3) When electron-donating substituent is present, intramolecular isomerization *via* H bonding is operative.

The halogenation of oximes has been applied to the preparation of nitro compounds,[1] halonitro paraffins,[2] and, in particular, hydroxamic halide derivatives. The conversion of oximes to hydroxamic chlorides *via* chlorination was studied in some detail[3] since this is the first step in the synthetic route to nitrile oxides for sterically unhindered compounds.[4] Grundman and Richter[4] reported that nitrile oxides could be prepared by dehydrogenation of the corresponding aldoximes with *N*-bromosuccinimide in *N*,*N*-dimethylformamide solution. The reaction apparently proceeded first to the hydroxamic bromide which was subsequently dehydrobrominated by the base to the nitrile oxide. Solvents such as chloroform,[3c,d,g,9] ether,[3a,5] or 8.3 *N* aqueous hydrochloric acid solution[3a,e] have been employed in the chlorination of oximes. It was found that aromatic aldoximes bearing bulky ortho substituents could not be chlorinated to hydroxamic chlorides without a considerable additional uptake of chlorine by the molecule, presumably by substitution in the aromatic ring.[6] Furthermore, strong electron-donating substituents in the aromatic nucleus facilitated chlorination of the ring with the result that a mixture of chlorinated products was formed.[3a]

I wish to report some interesting results which were discovered in the course of investigating the chlorination of oximes. It was found that substituted aromatic oximes, especially in the presence of a nitro group in the ring, gave the corresponding benzal chloride derivatives upon treatment with chlorine in methylene chloride or pure chloroform solution at -20 to $0°$. However, when commercial (comm) chloroform[7] or methylene chloride which contained 0.75% ethanol was used as the solvent (at -15 to $20°$), substituted benzhydroxamic chlorides were obtained. For the purpose of mechanistic study of benzal chloride formation, a systematic investigation of the chlorination of oximes in commercial chloroform and methylene chloride was undertaken. The results were summarized in Table I.[8-10]

The use of benzhydroxamic chloride and its derivatives as precursors for 1,3-dipolar addition reactions has been studied extensively for the past 10 years. In spite of the wide application of benzhydroxamic chlo-

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(2) E. M. Cherkasova and N. N. Mel'nikov, *Zh. Obshch. Khim.*, **19**, 321 (1949); *Chem. Abstr.*, **43**, 6569*a* (1949).

(3) See, for example (a) R. H. Wiley and B. J. Wakefield, *J. Org. Chem.*, **25**, 546 (1960); (b) B. G. Bowenlock and W. Luttke, *Quart. Rev., Chem. Soc.*, **12**, 321 (1958); (c) J. T. Hackmann and P. A. Harthoorn, British Patent 949,371 (1964); (d) T. Farley, F. H. Rathmann, and D. Tangen, *Proc. N. D. Acad. Sci.*, **13**, 61 (1959); (e) G. W. Perold, A. P. Steyn, and F. V. K. von Reiche, *J. Amer. Chem. Soc.*, **79**, 462 (1957); (f) M. H. Benn, *Can. J. Chem.*, **42**, 2393 (1963).

(4) C. Grundmann and R. Richter, *J. Org. Chem.*, **33**, 476 (1968), and other papers in this series.

(5) G. Casnati and A. Ricca, *Tetrahedron Lett.*, No. 4, 327 (1967).

(6) C. Grundmann and J. M. Dean, *J. Org. Chem.*, **30**, 2809 (1965).

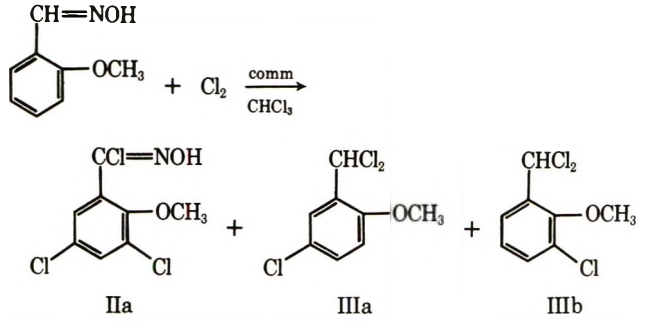
(7) Commercial chloroform (reagent grade) contains 0.75% ethanol as stabilizer (purchased from Matheson Coleman and Bell, East Rutherford, N. J.). It is purified by the method of L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath, Boston, Mass., 1955, p 283.

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

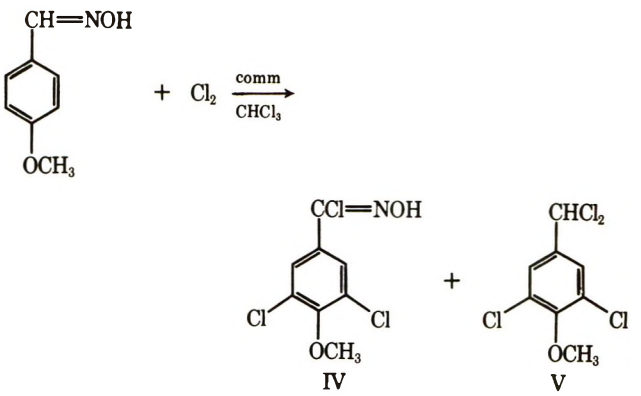
(9) G. Bianchetti, D. Pocar, and P. D. Croce, *Gazz. Chim. Ital.*, **93**, 1714 (1963); *Chem. Abstr.*, **60**, 14500*h* (1964).

(10) E. H. Huntereess, "Organic Chlorine Compounds," Wiley, New York, N. Y., 1948, pp 889, 895.

ride (I) and its derivatives, the basic methods for preparation of these compounds are limited only to two variations, *i.e.*, (1) chlorination of oximes in *ca.* 8.3 *N* hydrochloric acid at 0°[11] and (2) chlorination of oximes in chloroform.[3g,12,13] Both methods were used for the preparation of I. It was found that I could best be prepared by using commercial chloroform as solvent and the pure compound was obtained by vacuum distillation (below 100°) instead of recrystallization from petroleum ether.[14] This compound decomposed upon standing in the atmosphere within several days. Identification was achieved by converting I to 3,4-diphenylfuroxan upon treatment with 10% aqueous sodium hydroxide solution.[3a] The use of a number of substituted benzhydroxamic chlorides as precursors for the preparation of nitrile oxides without describing a method of preparation has been disclosed.[3a,15,16] In general, chloro- and nitro-substituted benzaldoximes gave benzhydroxamic chloride derivatives in 27–59% yield when commercial chloroform was employed as solvent for the chlorination process. *o*-Nitrobenzaldoxime failed to give the hydroxamic chloride derivative upon chlorination. Instead, a yellow oily residue was collected after work-up. A violent explosion occurred in the course of vacuum distillation (pot temperature 130°). When *o*-methoxybenzaldoxime was chlorinated in commercial chloroform, a mixture of substituted benzhydroxamic chloride IIa (11%) and benzal chloride IIIa and IIIb (58%) was obtained. The isomeric

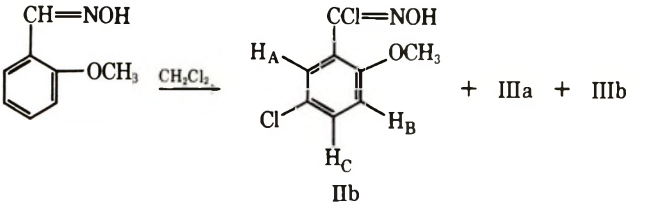


3-chloro- (IIIb) or 5-chloro-2-methoxybenzal chloride (IIIa) could not be separated into its components. The isomeric mixture was collected from vacuum distillation and gave satisfactory elemental analysis. The nmr spectrum showed a ratio of 1:1.16, which was calculated from the methoxy signal (δ 4.10, 4.18) for these two isomeric products. Similarly, chlorination of *p*-methoxybenzaldoxime resulted in 11% of 3,5-dichloro-4-methoxybenzhydroxamic chloride (IV) and 22% of 3,5-dichloro-4-methoxybenzal chloride (V) in commercial chloroform. The structure of V was assigned on the basis of the infrared (ir) and nmr spectra. It decomposed rapidly in the sealed tube under nitrogen atmosphere and did not give correct elemental analysis. The aromatic and methoxy protons appeared as singlets at δ 7.88 and 4.26, respectively. The benzal proton gave a sharp singlet at δ 6.94. Hence, the nmr spectrum was completely consistent with the assigned

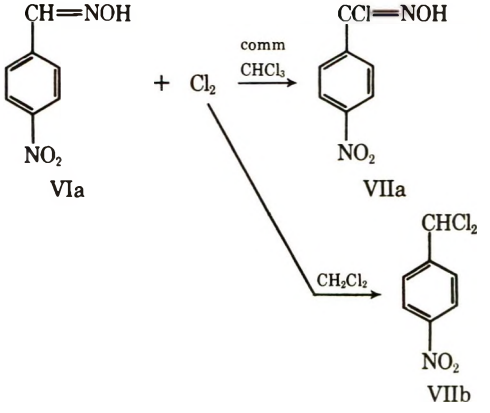


structure. The lack of hydroxy absorption in the ir spectrum further supported this fact.

The chlorination of oximes in methylene chloride is particularly interesting. The nitro-substituted benzaldoximes gave benzal chloride derivatives as the final product in 37–80% yield. On the other hand, chloro- and methoxy-substituted benzaldoximes yielded mixtures of benzhydroxamic chloride and benzal chloride derivatives. The chlorination of *o*-methoxybenzaldoxime in methylene chloride gave 5-chloro-2-methoxybenzhydroxamic chloride (IIb) together with



a mixture of IIIa and IIIb. In contrast to the chlorination in chloroform, monosubstituted benzhydroxamic chloride was obtained. It is interesting to note that chlorination of *p*-methoxybenzaldoxime in methylene chloride also gave a monosubstituted derivative, *i.e.*, 3-chloro-4-methoxybenzhydroxamic chloride. The structure has been proven by the chemical evidence (see part II in this series). The structure of IIb was assigned on the basis of elemental analysis and ir and nmr spectra. The nmr spectrum gave a methoxyl signal at δ 3.90 (s) and a hydroxy peak at δ 2.96. Proton signals in the aromatic region were at δ 7.17 (d, J = 9 cps, H_B) and δ 7.46 (m, H_A and H_C). It was noted that the yield for *o*- and *p*-methoxybenzhydroxamic chloride derivatives markedly increased from 5 to 22% and 11 to 53%, respectively, in the presence of triethylamine. Furthermore, *p*-nitrobenzhydroxamic chloride (VIIa) was the sole product (52% yield) upon



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(12) N. Singh, J. S. Dandhu, and S. Mahon, *Tetrahedron Lett.*, 4453 (1968), and references cited therein.
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(14) M. H. Benn, *Can. J. Chem.*, **42**, 2393 (1964).
(15) P. Rajagopalan and C. N. Talaty, *Tetrahedron Lett.*, 2101 (1966).
(16) A. Dondone, *ibid.*, 2397 (1967).

TABLE I

PRODUCTS FROM THE CHLORINATION OF OXIMES

Oximes	Solvent–catalyst	Reaction temp, °C	Products	Mp or bp (mm), °C, $n^{T}D$	Yield, %	C, % Obsd	C, % Calcd	H, % Obsd	H, % Calcd	N, % Obsd	N, % Calcd	Cl, % Obsd	Cl, % Calcd
Benzaldoxime	Comm $CHCl_3$	−15 to −20	Benzhydroxamic chloride	50–51 (*ca.* 45)[3a] 49[3g])	54								
o-Nitrobenzaldoxime	CH_2Cl_2	0	*o*-Nitrobenzal chloride	113 (2.5) [143–144 (12)[8]], $n^{19}D$ 1.5773	80							34.31	34.42
m-Nitrobenzaldoxime	CH_2Cl_2	0	*m*-Nitrobenzal chloride	66–67 (65)[8]	33							34.56	34.42
	Comm $CHCl_3$	−15 to −20	*m*-Nitrobenzhydroxamic chloride	101–102 (96–97)[8a]	58							17.82	17.68
p-Nitrobenzaldoxime	CH_2Cl_2	0	*p*-Nitrobenzal chloride	43–44 (46)[8]	20–66							34.38	34.42
	CH_2Cl_2–dark	0	*p*-Nitrobenzal chloride		44								
	Pure $CHCl_3$	−15 to −20	*p*-Nitrobenzal chloride		50								
	Comm $CHCl_3$	−15 to −20	*p*-Nitrobenzhydroxamic chloride	126–127 (116)[9]	59	42.09	41.91	2.39	2.51	13.96	13.97	17.71	17.68
	CH_2Cl_2–Et_3N	0	*p*-Nitrobenzhydroxamic chloride		52								
	CH_2Cl_2–0.75% EtOH	0	*p*-Nitrobenzhydroxamic chloride		77								
	CH_2Cl_2–0.75% EtOH	−15 to −20	*p*-Nitrobenzhydroxamic chloride		52–59								
6-Nitroveratraldoxime	CH_2Cl_2	0	6-Nitro-3,4-dimethoxybenzal chloride	109–110	37	40.72	40.62	3.41	3.41	5.20	5.27	26.15	26.65
2,4-Dinitrobenzaldoxime	CH_2Cl_2	0	2,4-Dinitrobenzal chloride	121 (0.03), $n^{19}D$ 1.6010	50	34.69	33.49	1.74	1.61	11.39	11.16	28.20	28.25
o-Chlorobenzaldoxime	CH_2Cl_2	0	*o*-Chlorobenzal chloride	53 (0.12), $n^{16}D$ 1.5661 [100 (10), $n^{16}D$ 1.5670][10]	61	43.33	43.52	2.52	2.02			52.81	54.46
	Comm $CHCl_3$	−15 to −20	*o*-Chlorobenzhydroxamic chloride	57–58	27	44.34	44.24	2.55	2.65	7.46	7.37	37.39	37.32
p-Chlorobenzaldoxime	CH_2Cl_2	0	*p*-Chlorobenzal chloride	93–94 (4), $n^{19}D$ 1.5672 [108 (10)][3a]	3–45	43.23	43.01	2.47	2.58			54.55	54.41
			p-Chlorobenzhydroxamic chloride	88–90 (82–86)[3a]	23–69							37.32	37.32
	Comm $CHCl_3$	−15 to −20	*p*-Chlorobenzhydroxamic chloride		51								

p-Methoxybenzaldoxime	CH_2Cl_2	0	3-Chloro-4-methoxybenzhydroxamic chloride	22							
			3,5-Dichloro-4-methoxybenzal chloride	40							
	CH_2Cl_2–Et_3N	−15 to −20	3,5-Dichloro-4-methoxybenzhydroxamic chloride	53	37.99	37.75	2.45	2.38	5.60	5.50	41.57 41.79
	Comm $CHCl_3$	−15 to −20	3,5-Dichloro-4-methoxybenzal chloride	22							
			3,5-Dichloro-4-methoxybenzhydroxamic chloride	11	97 (0.03), $n^{24}D$ 1.6728						
o-Methoxybenzaldoxime	CH_2Cl_2	0	3-Chloro- and 5-chloro-2-methoxybenzal chloride	26	42.29	42.61	2.91	3.13			47.32 47.17
			5-Chloro-2-methoxybenzhydroxamic chloride	5	79–82 (0.03), $n^{24}D$ 1.5658						
	CH_2Cl_2–Et_3N	−15 to −20	5-Chloro-2-methoxybenzhydroxamic chloride	22	143–145		43.82	43.66	3.19	3.21	6.26 6.37
	Comm $CHCl_3$	−15 to −20	3,5-Dichloro-2-methoxybenzhydroxamic chloride	11	130–132		37.98	37.75	2.39	2.38	5.53 5.50
			3-Chloro- and 5-chloro-2-methoxybenzal chloride	58							42.28 41.79

chlorination when triethylamine was added to a methylene chloride solution of *p*-nitrobenzaldoxime (VIa). Thus, in the presence of an equivalent amount of triethylamine, benzhydroxamic chloride derivatives became the only isolable chlorination product. When VIa was chlorinated in pure chloroform or methylene chloride, *p*-nitrobenzal chloride (VIIb) was obtained in 50 and 66% yield, respectively; no VIIa was isolated from the reaction mixture. It is concluded that the presence of 0.75% ethanol had altered the reaction pathway. This fact was further proved by using methylene chloride which contained 0.75% ethanol as reaction solvent. A 77% yield of VIIa was obtained when VIa was chlorinated under these conditions. The chlorination of *p*-chlorobenzaldoxime (VIb) was studied by varying reaction time at 0° with methylene chloride as solvent. The results were listed in Table II.

TABLE II

PRODUCT DISTRIBUTION FROM THE CHLORINATION OF VIb

Reaction time, hr, at 0°	VIIIa, %	VIIIb, %	VIIIa/VIIIb
0	23	34	0.68
1	63	8	7.88
2	41	18	2.28
3	57	32	1.78
5	38	45	0.84

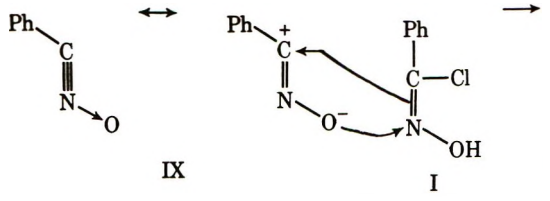
When the reaction mixture was warmed to *ca.* 50° in a water bath immediately after addition of chlorine (*i.e.*, 0-hr reaction time), the yield of *p*-chlorobenzhydroxamic chloride (VIIIa) was reduced to a minimum. It is obvious that the optimal condition for the formation of VIIIa is 1 hr at 0° of cooling.

I have examined the chlorination of benzaldoxime and *o*-hydroxy- (XI) and *p*-dimethylaminobenzaldoxime (XVII) in methylene chloride solution. The reaction products from chlorination of benzaldoxime were formulated as follows.

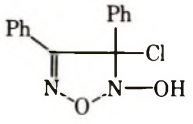
X

The formation of *O*-benzoylbenzhydroxamic chloride will be explained in detail in a subsequent paper. Benzonitrile, which formed as a result of dehydration, was obtained in 23% yield upon vacuum distillation as the low-boiling fraction. A crystalline material was collected from the high-boiling fraction by filtration. After several recrystallizations from ethyl acetate, 2-hydroxy-3,4-diphenyl-3-chloro-1,2,5-Δ^4-oxadiazoline (X) was obtained. On the basis of ir, ultraviolet (uv), and mass spectra, the structure of X was proposed. The mass spectrum of X showed, in addition to the weak molecular ion at *m/e* 274 (2%), an ion at *m/e* 103 (intensity 100%) corresponding to the benzonitrile ion. Fragments were also present corresponding to the benzonitrile *N*-oxide (IX) (*m/e* 119, 55%) and benzhydrox-

amic chloride (*m/e* 155, 9%) ions. In view of the uv spectrum of 3,4-diphenylfuroxan [λ_{max}^{EtOH} 237 mμ (ε 27,223), 280 (8831)], the absorption of λ_{max}^{EtOH} 258 mμ (ε 19,900) for X indicates the presence of a $C_6H_5CH{=}N$ chromophore.[3e,17,18] Barnes, Pinkeny, and Phillips[19] examined the ir absorption of isoxazolines and attributed strong absorption found at 1710 cm^{-1} (in dioxane solution) to the C=N-grouping, though the summary given by Bellamy[20] leads one to expect specific absorption for the -C=N-grouping around 1660 cm^{-1}. Thus, the strong ir band at 1735 cm^{-1} for X is ascribed as C=NO- absorption.[21] Compound X probably resulted from the reversed addition of IX to I, *i.e.*,

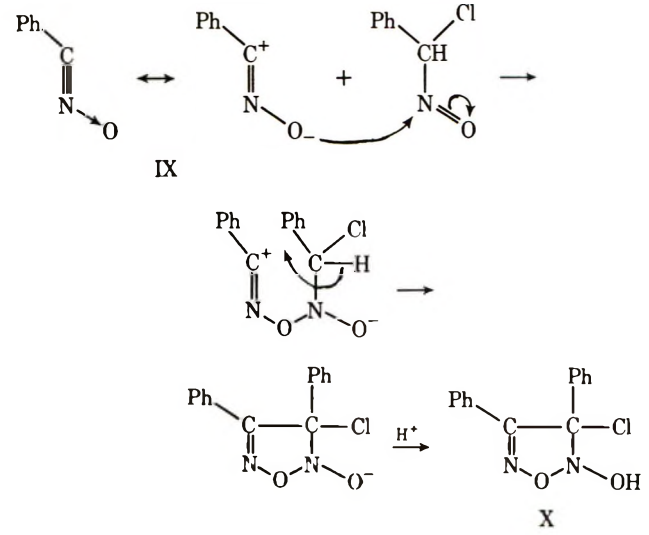


IX I



X

It is reported that the addition of IX to I[22] and to benzaldoxime in the presence of boron trifloride[23] occurred in conventional fashion. The exact nature of this reversed addition is unknown. A plausible explanation is the addition of IX to the nitroso tautomer, *i.e.*,



IX X

It is noted that the positive character of the nitrogen atom in the nitroso compound is greatly enchanced by the oxygen atom in comparison to I.

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(20) L. J. Bellamy, "The Infrared Absorption of Complex Molecules," Methuen and Co. Ltd., London, 1954, p 223.

(21) G. Bianchi and E. Frati, *Gazz. Chim. Ital.*, **96**, 559 (1966); *Chem. Abstr.*, **65**, 7160*g* (1966).

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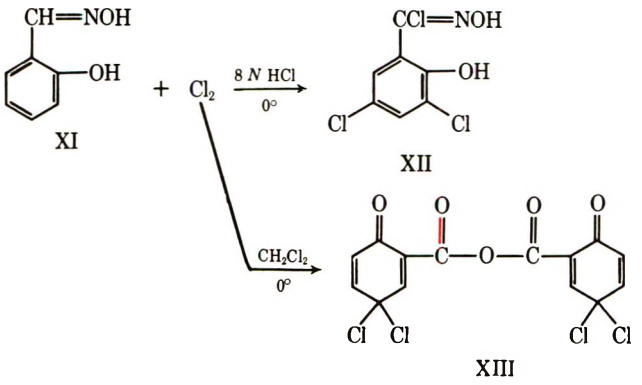
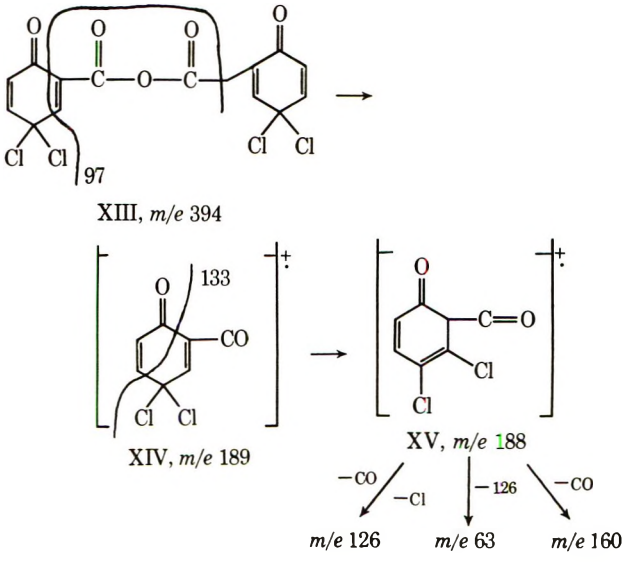
(23) S. Morrocchi and A. Ricca, *Chim. Ind. (Milan)*, **49**, 629 (1967); *Chem. Abstr.*, **67**, 907374 (1967).

Wiley and Wakefield[3a] reported that 3,5-dichloro-2-hydroxybenzhydroxyamic chloride (XII) was obtained upon chlorination of *o*-hydroxybenzaldoxime (XI) in 8 *N* hydrochloric acid at 0°. When XI was chlorinated in methylene chloride, XIII was collected as the reaction product. No hydroxamic chloride derivative was isolated from the reaction mixture. The assignment of structure XIII is made by examination of the ir, uv, and mass spectra. The uv spectrum showed an absorption at λ_{max}^{EtOH} 222 mμ (ε 21,600) and 342 (3250) which represent the presence of an α,β-unsaturated ketone.[24] The absorption at λ_{max}^{EtOH} 258 mμ (ε 6000) is indicative of the presence of a disubstituted α,β-unsaturated ketone [HC(C=O)=C—C=O]. The ir absorption at 1665 cm^{-1} is also attributed to the α,β-unsaturated ketone.[20] In addition, the cis-disubstituted ethylene (HC=CH) absorbs at 702 cm^{-1}. Scheme I presents what appears to be the most reasonable fragmentations which account for the mass spectrum. The ir spectrum has no hydroxyl absorption and the carbonyl group absorbed at 1665 cm^{-1} with two shoulders at 1660 and 1650 cm^{-1}. Fragments of *m/e* 133 (8%) and 97 (8%) further supported the proposed structure. The mechanism of formation of XIII is unknown. Similarly, the chlorination of *p*-dimethylaminobenzaldoxime (XVII) in methylene chloride gave an interesting product instead of the expected benzhydroxamic chloride derivative. A small amount



XI XII XIII

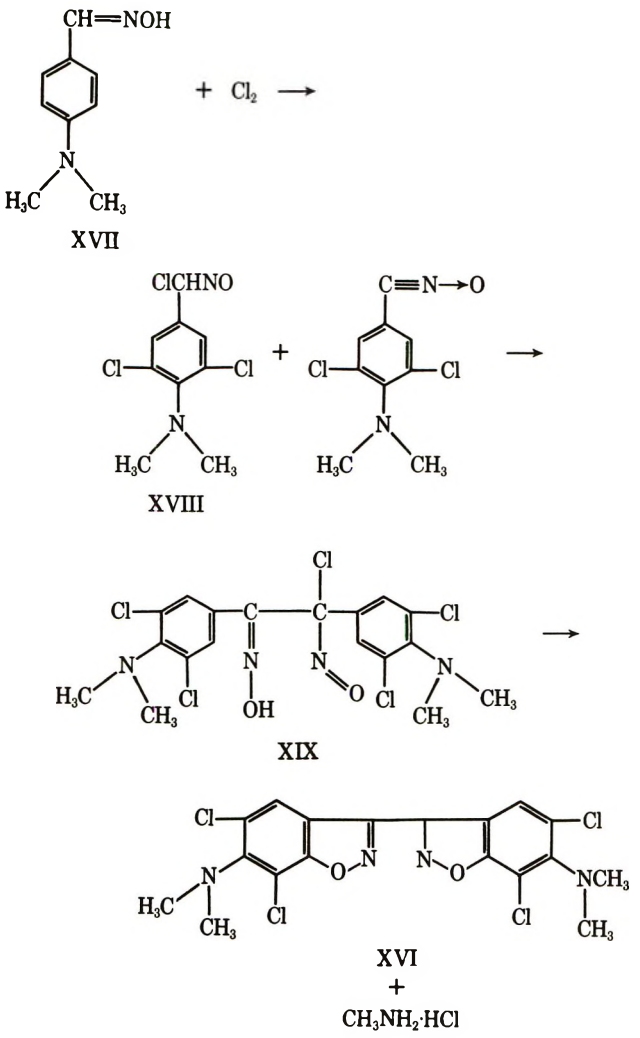
SCHEME I



XIII, *m/e* 394 XIV, *m/e* 189 XV, *m/e* 188 *m/e* 126 *m/e* 63 *m/e* 160

(24) R. B. Woodward, *J. Amer. Chem. Soc.*, **63**, 1123 (1941).

of methylamine hydrochloride was also isolated. Compound XVI was obtained in 6% yield and its structure



was assigned with the aid of uv, ir, nmr, and mass spectra. The spectrum of XVI consists of a singlet at δ 7.68 (aromatic proton) and two singlets centered at δ 2.95 (*N*-methyl proton). The mass spectrum of XVI showed a parent peak at *m/e* 460 (28%) and a base peak at *m/e* 400 ($M^+ - 2NO$) (intensity 100%). Cleavage of the central carbon–carbon bond gave a molecular ion *m/e* 230 (54%) corresponding to the monomer of XVI. The presence of the dimethylamino group is suggested by the occurrence of *m/e* 44 (28%) ion. The only other fragments of significant intensity corresponded to $M^+ -$ oxygen (19%), $^1/_2M^+ -$ OH (90%), and $^1/_2M^+ -$ CN (78%). These facts eliminated the possibility that XVI was a 3,4-diarylfuroxan derivative. The ir spectrum showed an absorption at 1600 cm^{-1} for the >C=N– group in contrast to 3,4-diphenylfuroxan which absorbs at 1575 and 1590 cm^{-1}. The presence of a substituted isoxazole system in XVI was indicated by its absorption at 952 cm^{-1}.[25] The uv spectrum also displayed marked differences between XVI and 3,4-diphenylfuroxan. It is surprising to find that the uv spectrum of XVI is quite different from those of the benzisoxazole derivatives reported by Casini *et al.*[26] The formation of XVI is visualized as the addition of nitrile *N*-oxide to the C–H bond of the chloronitroso intermediate XVIII. The final product was obtained by the ring closure of the chloronitroso intermediate XIX. The origin of the isolated methylamine hydrochloride is unknown.

In the hope of better defining the intricacy and complexity involved in the chlorination of oximes, I have reported the chlorination of benzaldoxime, XI, and XVII in methylene chloride solution. It is emphasized that the author made no attempt to clarify the exact nature of this reaction but to call attention to the paucity of mechanistic study on this complicated chlorination process. The solvent effect of this chlorination reaction is remarkable. The change from a polar solvent to a nonpolar one could alter the entire reaction pathway.[3a,c,d,e,g,5,9] This new reaction evidently provides a highly convenient route to benzal chlorides which are not readily accessible by conventional methods. For example, 2,4-dinitrobenzal chloride, which could not be prepared by the reaction of phosphorus pentachloride and the corresponding aldehyde,[27] is readily prepared by this method in 50% yield.

In 1958 Gowenlock and Lüttke[28] called attention to the paucity of kinetic data on the isomerization (to oxime) of primary and secondary aliphatic nitroso compounds. The amine-catalyzed isomerization of nitrosocyclohexane to oxime was reported by DiGiacomo.[29] Two possible mechanism consistent with the kinetic data were proposed by the author. The intermediacy of the amine–nitroso monomer complex is suggested. It has been shown that the rate constant increased with decreasing solvent polarity. The mechanistic study of the isomerization of aromatic nitroso compounds to oximes was largely limited to the qualitative observation that blue or green solutions of nitroso compounds gave, on standing, colorless solutions of the corresponding oximes. The mechanism of benzhydroxamic chloride formation has been demonstrated to be a two-stage process consisting of halogenation and subsequent isomerization of the secondary nitroso compound formed.[28] The addition of chlorine to oxime proceeding to the chloronitroso compound in the absence of light was reported by Muller and Metzger.[30] While the isomerization of primary and secondary *C*-nitroso compounds to the benzhydroxamic chloride is well known, the mechanism of benzal chloride formation is relatively obscure. Based on the following chemical evidence in combination with the spectroscopic study of VIa and VIb, it is concluded that the formation of benzal chloride derivatives also proceeds through a *C*-nitroso intermediate XX.

(1) An aliquot of mixture of VIa or VIb and chlorine in methylene chloride gave a positive Liebermann test for nitroso compounds.[31]

(2) Compound VIIa was the sole product (52% yield) upon chlorination when triethylamine was added to a methylene chloride solution of VIa. It is obvious that the base-catalyzed isomerization had altered the reaction pathway.

(25) W. B. Renfrow, J. F. Witte, R A. Wolf, and N. R. Bohl, *J. Org. Chem.*, **33**, 150 (1968).

(26) G. Casini, F. Gualtieri, and M. L. Stein, *J. Heterocycl. Chem.*, **6**, 279 (1969).

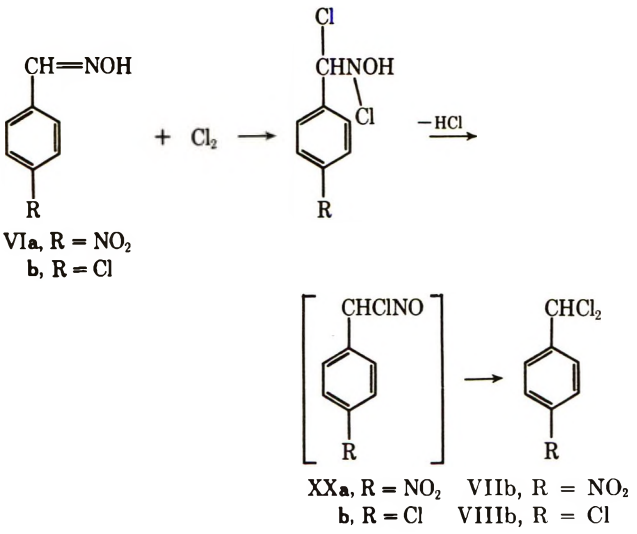
(27) The preparation of this compound has been claimed without describing any physical constants: *Beilstein*, 2nd ed **5**, 265 (1956).

(28) (a) R. H. Wiley and B. J. Wakefield, *J. Org. Chem.*, **25**, 546 (1960); (b) B. G. Gowenlock and W. Lüttke, *Quart. Rev., Chem. Soc.*, **12**, 321 (1958).

(29) A. DiGiacomo, *ibid.*, **30**, 2614 (1965).

(30) E. Muller and H. Metzger, *Chem. Ber.*, **88**, 165 (1955).

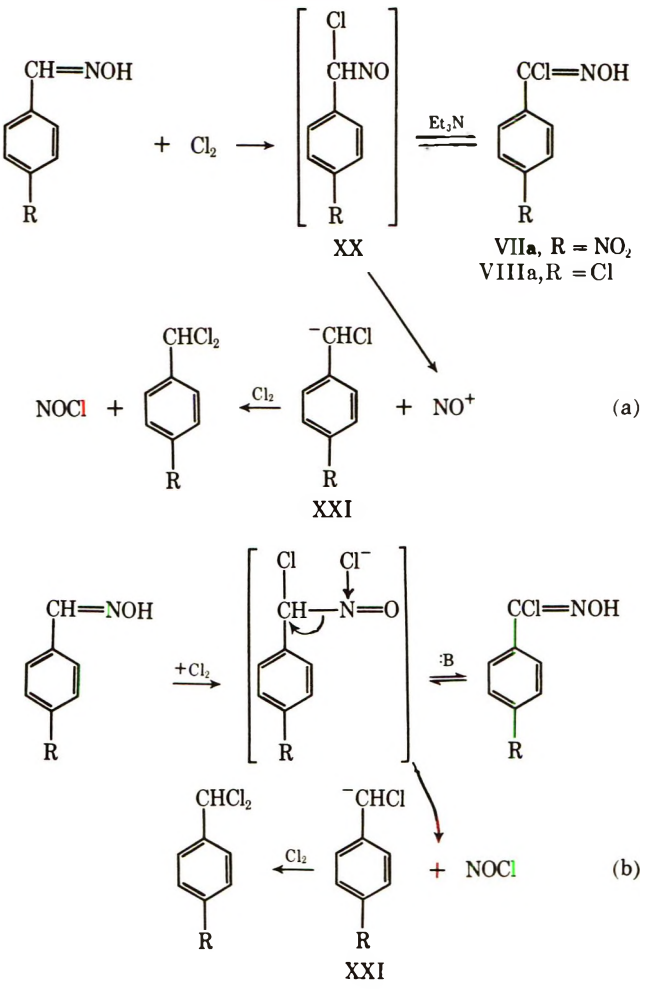
(31) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," 2nd ed, Interscience, New York, N. Y., 1957.



(3) The visible spectra of the mixture of VIa or VIb and chlorine showed an absorption at $\lambda_{max}^{CH_2Cl_2}$ 635 mμ and 640, respectively. This fact is indicative of the presence of a *C*-nitroso intermediate.[28] The infrared of the mixture showed the –N=O stretching frequency at 1525 cm^{-1} and the –CN– frequency at 1015, 824, and 770 cm^{-1}.[28,32] A crude estimation of the concentration of intermediate XXb in the reaction mixture was attempted. The relatively stable XXb was chosen for this purpose. Since it was observed qualitatively, *i.e.*, the blue solution, which was assumed to be due to this *C*-nitrosocompound, does not discolor at 0° for at least 3 hr. In the case of XXa, the blue color disappeared within 0.5 hr. The extinction coefficient of the closely related *p*-chloronitrosobenzene [λ_{max} 750 mμ (ϵ 45.5)][33] was taken as standard. The extinction coefficient of XXb is expected to be smaller than *p*-chloronitrosobenzene. It is found that a minimum of 38.6% of XXb is formed immediately after addition of chlorine.

(4) Upon treatment with chlorine in methylene chloride solution, VIIIa could not be converted to VIIa. Furthermore, when chlorination of VIa in methylene chloride solution was carried out in darkness, 44% of VIIIa was obtained showing that the loss of NO is not a free-radical reaction. In view of the evidence listed above, the reaction mechanisms shown in Scheme II are proposed for the formation of benzal chloride. The mechanism described in eq a suggested that the intermediate XX decomposed unimolecularly to give carbanion XXI and a nitrosyl ion. The carbanion XXI and nitrosyl ion in turn reacted with 1 mol of chlorine to give the final products. The second proposed mechanism, formulated in eq b, has been considered as a nucleophilic displacement on the nitroso group, perhaps by chloride ion, and that carbanion XXI and nitrosyl chloride are thereby produced. The presence of nitrosyl chloride was demonstrated by trapping with an aqueous aniline hydrochloride–hydrochloric acid solution. The resulting benzenediazonium chloride coupled with phenol in alkaline solution very rapidly at ice bath temperature to form an orange-colored solution which is indicative of the presence of *p*-hydroxyazobenzene.[34] The proposed nitrosyl ion formation was further supported by the fact that an absorption maximum of 440 mμ, which is indicative of nitrosyl ion absorption, was observed from an aliquot of the reaction mixture between VIa and chlorine in methylene chloride.[35]

SCHEME II



Invariably in methylene chloride solution, nitro-substituted oximes gave the benzal chloride as the final product. The carbanion XXI is probably stabilized by nitro substituents through inductive and/or conjugative effects.[36]

The chloro derivatives resulted in a mixture of VIIb and VIIIb and the ratio of these two products was determined by the cooling period after addition of chlorine (see Table II). However, when methoxy-substituted oximes were chlorinated under these conditions, benzal chloride derivatives became the predominant product irrespective of the solvent used (commercial chloroform or methylene chloride). The stabilization of a carbanion by nitro groups in the ortho or para positions is known while a carbanion stabilized by a chloro group through an inductive effect is also reported.[36] It is well known that the methoxy group destabilizes carbanions. The evidence cited clearly indicates that α-chloro-α-nitroso intermediate XX is

(32) W. Lüttke, *J. Phys. Radium*, **15**, 633 (1954); *Chem. Abstr.*, **52**, 17960e (1958).

(33) K. Nakamoto and R. E. Rundle, *J. Amer. Chem. Soc.*, **78**, 1113 (1956).

(34) L. F. Fieser and M. Fieser, "Organic Chemistry," 3rd ed, Reinhold, New York, N. Y., 1956, p 618.

(35) L. J. Beckham, W. A. Fessler, and M. A. Kise, *Chem. Rev.*, **48**, 334 (1951).

(36) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 60.

the precursor for benzal chloride derivative formation. Thus, the variation in final product between nitro- and methoxy-substituted oximes must depend on the isomerization state. It is interesting to note that there is competition between elimination of a proton (see below) or nitrosyl ion from XX. Attention is called to the product distribution from the chlorination of VIb (see Table II). The ratio of VIIIa/VIIIb reached a maximum at 1 hr of the reaction time and decreases progressively as the reaction time increases. There is little difference between product ratio and reaction time when nitro- or methoxy-substituted oximes were chlorinated at various different reaction times. The balance of inductive and conjugative effects of the chloro-substituent in VIa enables one to speculate about the conditions favorable for the elimination of nitrosyl ion. It is conceivable that the presence of XX for extended periods, *i.e.*, by depressing the rate of isomerization by cooling, favors the elimination of nitrosyl ion.

The data presented in Table II concerning the products observed upon chlorinating VIb as a function of time reveals that (disregarding the 0-hr point) the formation of VIIIb is a linear function of time which can be described by the following equation (see Figure 1).

$$\% \text{ VIIIb} = 9.17 \times \text{time (in hours)}$$

The linear correlation between the per cent yield of VIIIb and time indicated that the formation of benzal chloride is a zero-order reaction. It is difficult to reconcile this fact with either of the mechanisms proposed previously. It is conceivable that the linear correlation is accidentally coincided with the formation of VIIIb. In order to verify the kinetic implication of data presented in Table II, a detailed study along this line is required.

Although the formation of nitrosyl ion from the electron impact of nitro compounds is well defined,[37] it is believed that this is the first example of the elimination of nitrosyl ion formation through the C–N heterolysis of a *C*-nitro compound.

The difference existing in final product between nitro-substituted and chloro- and methoxy-substituted oximes upon chlorination in methylene chloride and commercial chloroform deserves some explanation. Previously, the difference was attributed to the effect of ethanol on the isomerization process. The mechanism of isomerication of aromatic oximes is scarcely known. The amine-catalyzed isomerization of nitroso cyclohexane to oximes[29] is the only work of this kind reported to date. It is significant to note that benzal chloride derivatives were isolated as the major product upon chlorination of methoxy-substituted oximes in commercial chloroform. In contrast, benzhydroxamic chloride derivatives were the sole product when nitro- or chloro-substituted oximes were chlorinated in commercial chloroform. Obviously, the ethanol-catalyzed isomerization is only effective in the presence of electron-withdrawing groups. Ethanol-catalyzed isomerization of XX to oxime was demonstrated by the fact that no hydroxamic chloride derivative was isolated upon removal of ethanol from commercial chloroform. Compound VIIb was isolated in 59% yield when the

(37) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, San Francisco, Calif., 1964, p 206.

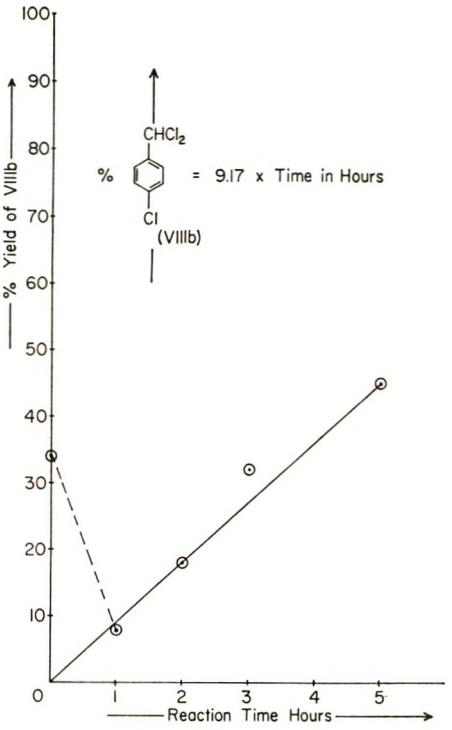


Figure 1.

chlorination of VIa was carried out in pure chloroform. On the basis of experimental results in hand, it is concluded that the isomerization process proceeds through three different pathways depending upon the catalyst and substituent in the benzene ring.

(1) Carbanion mechanism with triethylamine as catalyst follows.

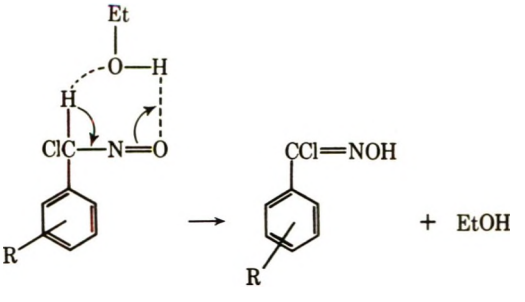
$$\text{ArCClNO} \xrightarrow{\text{Et}_3\text{N}} \text{ArC}^-\text{ClNO} + \text{Et}_3\text{NH}^+ \quad (1)$$

$$\text{ArC}^-\text{ClN}{=}\text{O} \longleftrightarrow \underset{\text{XXII}}{\text{ArCCl}{=}\text{NO}^-} \quad (2)$$

$$\text{ArCCl}{=}\text{NO}^- + \text{Et}_3\text{NH}^+ \longrightarrow \text{ArCCl}{=}\text{NOH} + \text{Et}_3\text{N}$$

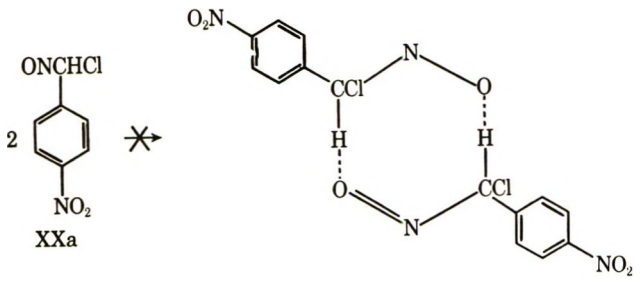
The fact that benzhydroxamic chloride derivatives were obtained after amine-catalyzed chlorination in all cases strongly supports the proposed mechanism. The abstraction of a proton from the chloronitroso compound resulted in a resonance stabilized anion (eq 2). The final product was obtained by protonation of anion XXII.

(2) Intermolecular H bonding mechanism with ethanol as catalyst follows.



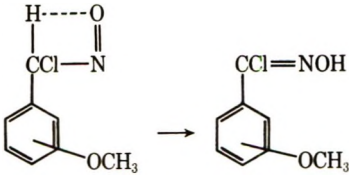
In the mechanism outlined, a cyclic intermediate was suggested for ethanol-catalyzed isomerization. It is expected that electron-withdrawing substituents such

as the nitro group would increase markedly the acidity of benzylic proton which becomes more susceptible to H bonding with ethanol. The absence of VII as the final chlorination product (in methylene chloride) of VIa is indicative of the lack of intermolecular H bonding between two molecules of XXa resembling the amine complex described by Giacomo.[29]



The lack of ethanol-catalyzed isomerization suggested that the methoxy-substituted α-chloro-α-nitroso compound is incapable of H bonding with ethanol due to an intramolecular H bonding (see below). Furthermore, the possibility of intermolecular H-bonding formation could also be excluded on this basis.

(3) The fact that chlorination of *o*- or *p*-methoxybenzaldoxime gave predominatly benzal chloride derivatives both in commerical chloroform and methylene chloride leads one to postulate the intramolecular isomerization mechanism for these compounds, *i.e.*,



The absence of intramolecular isomerization for XX is assumed to be due to the electron-withdrawing effect of the nitro group which reduces the electron density around nitrosyl oxygen.

Thus, the absence of benzhydroxamic chloride formation upon chlorination of VIa in methylene chloride is attributed to the incapability of intramolecular H bonding of XXa. Similarly, predominant benzal chloride formation as chlorination product for methoxy-substituted oximes could be explained on the basis of a slow intramolecular isomerization process.

The mechanisms cited above were based solely on product analysis. Further kinetic and stereochemical studies of oximes in relation to products will probably shed more light on the exact nature of the elimination and isomerization processes.

Experimental Section

The melting points were obtained on a Fisher-Jones melting point apparatus and are uncorrected, as are the boiling points. Ir spectra were recorded on a Perkin-Elmer Infracord Model 137 sodium chloride spectrophotometer. Uv spectra were obtained on a Coleman-Hitachi 124 double beam spectrophotometer in absolute ethanol. The nmr spectra were obtained with a Varian A-60A spectrometer using tetramethylsilane as internal standard. Mass spectra were taken on a Hitachi Perkin-Elmer RMV-7 mass spectrometer using an all-glass inlet. The microanalysis of the compounds were performed by Geller Microanalytical Laboratories, Saddle River, N. J. 07458.

Oximes.—Benzaldoxime was purchased from K & K Laboratories, Inc., Plainview, N. Y., as a mixture of α and β isomers. The other oximes were prepared by the hydroxylamine hydrochloride–sodium acetate method.[38]

Chlorination of Oximes. General Procedure.—Substituted benzaldoxime (5 g) was dissolved in 400 ml of methylene chloride at −20 to 0°. Chlorine gas was passed through this solution at a slow rate for 20 min. After standing in a cooling bath for 2 hr and then at room temperature overnight, air was bubbled through the reaction mixture until all the excess chlorine was removed. The solvent was removed under reduced pressure and the residue crystallized from the proper solvent or vacuum distilled if appropriate. Substituted benzal chlorides were isolated as the final product. When commercial chloroform was used as solvent, the same procedure was applied except that the reaction temperature was maintained at −15 to −20°. The product under these conditions was the benzhydroxamic chloride derivative. The individual oximes chlorinated by the above methods are listed in Table I. *Extra caution must be taken when liquid products are distilled at reduced pressure and high temperature (over 100°). In the case of o-nitrobenzaldoxime, a violent explosion occurred during vacuum distillation (pot temperature 130°).*

Preparation of 3,4-Diphenylfuroxan.[3a]—Benzhydroxamic chloride (2 g, 0.013 mol) was dissolved in 50 ml of ether. The solution was cooled in ice and an excess of 10% aqueous sodium hydroxide (10 ml) was added dropwise, with shaking. The solution was shaken occasionally for 30 min at 0°. The ether layer was separated and dried over anhydrous sodium sulfate. The ether solution was allowed to stand over the weekend at room temperature and condensed. The residual solid was crystallized from ethanol to give 0.77 g (64%), mp 117–118° (lit.[3a] 114–115°), of the desired product: ir (Nujol) 1575 and 1590 cm^{-1} (>C=N–); uv λ max 237 and 280 mμ (ε 27,223 and 8831, respectively).

Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.50; H, 4.23; N, 11.76. Found: C, 70.37; H, 4.25; N, 11.73.

Chlorination of Benzaldoxime in Methylene Chloride.—The benzaldoxime (a mixture of α and β isomers) (10 g, 0.0526 mol) was dissolved in 400 ml of methylene chloride at 0°. Chlorine gas was passed through this solution for 30 min. After being allowed to stand in an ice-water bath for 2 hr the reaction mixture was left at room temperature overnight. The excess chlorine was removed by bubbling air through this solution. The solvent was removed *in vacuo* and the residue was vacuum distilled. Benzonitrile was collected in 23% yield [1.96 g, bp 74–81° (0.8 mm)] as the low-boiling fraction. The crystalline material obtained from the high-boiling fraction [bp 110–111° (0.8 mm)] was collected by filtration and crystalized from ethyl acetate: 1.07 g (9%); mp 136–137° of X obtained; ir spectrum (Nujol) 3260 (OH) and 1735 cm^{-1} (PhC=N); uv spectrum λ max 258 mμ (ε 19,900, PhC=N); mass spectrum *m/e* (rel intensity) 274 (2) (parent peak), 155 (9.1), 119 (55), and 103 (100).

Anal. Calcd for $C_{14}H_{11}N_2ClO_2$: C, 61.21; H, 4.04; N, 10.20; Cl, 12.91. Found: C, 61.33; H, 3.89; N, 10.18; Cl, 12.91.

The solid residue (after vacuum distillation) was extracted with ether and the ether insoluble solid was crystallized from ethanol to give 1.15 g (12%), mp 109–110° (lit.[39] 109°), of *O*-benzoylbenzhydroxamic chloride: ir spectrum (Nujol) 1760 cm^{-1} (C=O); uv λ max 260 mμ (ε 25,714, PhC=N); mass spectrum *m/e* (rel intensity) 259 (2) (parent peak), 204 (15), 138 (3), 122 (27), 119 (10) 105 (100), and 103 (100).

Anal. Calcd for $C_{14}H_{10}NClO_2$: C, 64.75; H, 3.88; N, 5.39; Cl, 13.66; mol wt, 260. Found: C, 64.58; H, 3.88; N, 5.20; Cl, 13.99; mol wt, 262 (vaporimetric).

Chlorination of *o*-Hydroxybenzaldoxime (XI) in Methylene Chloride.—XI (2 g, 0.0146 mol) was dissolved in 250 ml of methylene chloride at 0°. Chlorine gas was passed through this solution for 15 min. After being allowed to stand in an ice-water bath for 2 hr, the reaction mixture was left at room temperature overnight. The excess chlorine was removed by bubbling air through this solution. The solvent was removed at reduced pressure and the oily residue was dissolved in 5 ml of ethanol. After standing at room temperature for several days, a crystalline material was collected from the ethanolic solution. The com-

(38) See ref 7, p 103.
(39) See ref 27, p 214.

pound was crystallized from 2-propanol: 176 mg (6%); mp 93–94° of XIII obtained; ir spectrum (Nujol) 1665, 1660 (shoulder), 1650 (shoulder) and 702 cm^{-1}; uv spectrum λ max 222 mμ (ε 21,600), 258 (6000), and 342 (3250); mass spectrum *m/e* (rel intensity) 189 (100), 188 (54), 160 (6), 142 (8.5), 133 (8), 126 (5.4), 97 (8), and 63 (13).

Anal. Calcd for $C_{14}H_6Cl_4O_5$: C, 42.46; H, 1.53; Cl, 35.81. Found: C, 42.72; H, 1.90; Cl, 35.89.

Chlorination of *p*-Dimethylaminobenzaldoxime (XVII) in Methylene Chloride.—XVII (2 g, 0.0122 mol) was dissolved in 300 ml of methylene chloride at 0°. Chlorine gas was passed through this solution for 15 min. After being allowed to stand in an ice–water bath for 2 hr, the reaction mixture was left at room temperature overnight. The excess chlorine was removed by bubbling air through methylene chloride solution. The solvent was removed under reduced pressure and the solid residue was crystallized from 2-propanol. The crystalline material was collected by filtration; 1.04 g was obtained. The crystalline material was recrystallized from 2-propanol; a small amount of methylamine hydrochloride, mp 232–233° (lit.[8] 226–228°), was obtained. When crystalline material was treated with 5% aqueous hydrochloric acid followed by extraction with methylene chloride, XVI was isolated in 6% (150 mg) yield, mp 161.5–162.5°. An analytical sample could be prepared by recrystallization from ethyl acetate: ir spectrum (Nujol) 1600 (>C=N) and 952 cm^{-1}; uv spectrum λ max 323 mμ (ε 1358) and 218 (5633); nmr (acetone-d_6) δ 7.68 (s, 1), 2.9 (s, 2), and 3.0 (s, 4); mass spectrum (rel intensity) *m/e* 460 (28) (parent peak), 444 (19), 400 (100), 230 (61), 213 (90), 204 (78), and 44 (28).

Registry No.—X, 29577-42-2; XIII, 29577-43-3; XVI, 29641-90-5; *o*-chlorobenzaldoxime, 3717-28-0; *p*-chlorobenzaldoxime, 3848-36-0; *p*-methoxybenzaldoxime, 3235-04-9; benzaldoxime, 932-90-1; *o*-nitrobenzaldoxime, 6635-41-2; *m*-nitrobenzaldoxime, 3431-62-7; *p*-nitrobenzaldoxime, 1129-37-9; 6-nitroveratraldoxime, 29577-51-3; 2,4-dinitrobenzaldoxime, 3236-33-7; *o*-methoxybenzaldoxime, 29577-53-5; *o*-chlorobenzhydroxamic chloride, 29568-74-9; 3,5-dichloro-4-methoxybenzhydroxamic chloride, 29568-75-0; 3,5-dichloro-4-methoxybenzal chloride, 29568-76-1; *o*-nitrobenzal chloride, 610-14-0; 6-nitro-3,4-dimethoxybenzal chloride, 29568-78-3; 2,4-dinitrobenzal chloride, 20195-22-6; 3-chloro-2-methoxybenzal chloride, 29568-32-9; 5-chloro-2-methoxybenzal chloride, 29568-33-0; 5-chloro-2-methoxybenzhydroxamic chloride, 29568-34-1; 3,5-dichloro-2-methoxybenzhydroxamic chloride, 29568-35-2; 3,4-diphenylfuroxan, 5585-14-8; *O*-benzoylbenzhydroxamic chloride, 29568-37-4.

Acknowledgments.—The author is grateful to Dr. Victor Hansen for helpful discussion throughout this work. Thanks are also due to Dr. A. K. Bose for the measurements of nmr and mass spectra.

Chlorination of Oximes. II. Pyrolysis of Benzhydroxamic Chloride Derivatives

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Received June 11, 1970

The pyrolysis of benzhydroxamic chloride derivatives (XVI) was investigated. It was found that thermolysis of XVI involved two reaction paths depending on the substituents on the aromatic ring. When benzhydroxamic chloride (II) and 3-chloro-4-methoxybenzhydroxamic chloride (IV) were pyrolyzed at 180°, isocyanate derivatives were obtained. On the other hand, nitro- (VIII and XIV) and chloro- (XV) substituted compounds gave *O*-benzoylbenzhydroxamic chloride derivatives as the major product and substituted benzonitriles were isolated as minor components. Based on the fact that rearrangement of II and IV gave isocyanate derivatives in combination with the isolation of nitrile derivatives from the reaction mixture, two reaction mechanisms were proposed for the pyrolytic process. A cyclic mechanism was proposed for the formation of *O*-benzoylbenzhydroxamic chloride (I) and its analogs. It is noted that the iminoxy radical addition mechanism cannot be excluded as an alternate pathway for the formation of I.

The formation of *O*-benzoylbenzhydroxamic chloride (I) as a by-product (12% yield) upon distillation of the chlorination product of benzaldoxime in methylene chloride was observed.[1] When the distillation process was carried out under low temperature (below 100°), no I was isolated from the reaction mixture. It was concluded that I must be the pyrolytic product of benzhydroxamic chloride (II). In order to understand the nature of this pyrolytic process, the pyrolysis of benzhydroxamic chloride derivatives was investigated.

In the thermolysis of II at 180° (8 mm), 70% of phenyl isocyanate and 21% of I was isolated. Similarly, 18% of 3-chloro-4-methoxyphenyl isocyanate (III) was obtained from the pyrolysis of 3-chloro-4-methoxybenzhydroxamic chloride (IV). On the other hand, nitro- and chloro-substituted benzhydroxamic chlorides gave a mixture of substituted benzonitrile and the corresponding *O*-benzoylbenzhydroxamic chloride derivatives. The results are formulated in Scheme I. The physical properties of substituted *O*-benzoylbenzhydroxamic chloride derivatives are summarized in Table I.

Phenyl isocyanate was characterized as *N,N*-diphenylurea after reacting with aniline. Compound III was converted to a urea derivative by an unambiguous route (Scheme I). This product proved to be identical with the compound obtained by the reaction of phenylisocyanate with 3-chloro-4-methoxyaniline as shown by mixture melting point and infrared (ir) spectrum. The structure of I was assigned on the basis of its ir, ultraviolet (uv), and mass spectra. The mass spectrum of I exhibited a weak molecular ion peak at *m/e* 259 (2%), two base peaks at *m/e* 105 (rel intensity 100%) and 103 (100%), and other prominent peaks at *m/e* 204 (15%) ($M^+ - Cl$), 138 (30%) (PhCCl=N), and 119 (10%) (PhC≡N→O). It is of interest to note that the spectrum also showed a strong peak at *m/e* 122 (27%) ($C_6H_4NO_2$). The exact course of the formation of this ion is not clear. Further evidence that I has the proposed structure was provided by its hydrolysis with aqueous alcoholic sodium hydroxide, which gave benzoic acid and II as final products. The high yield

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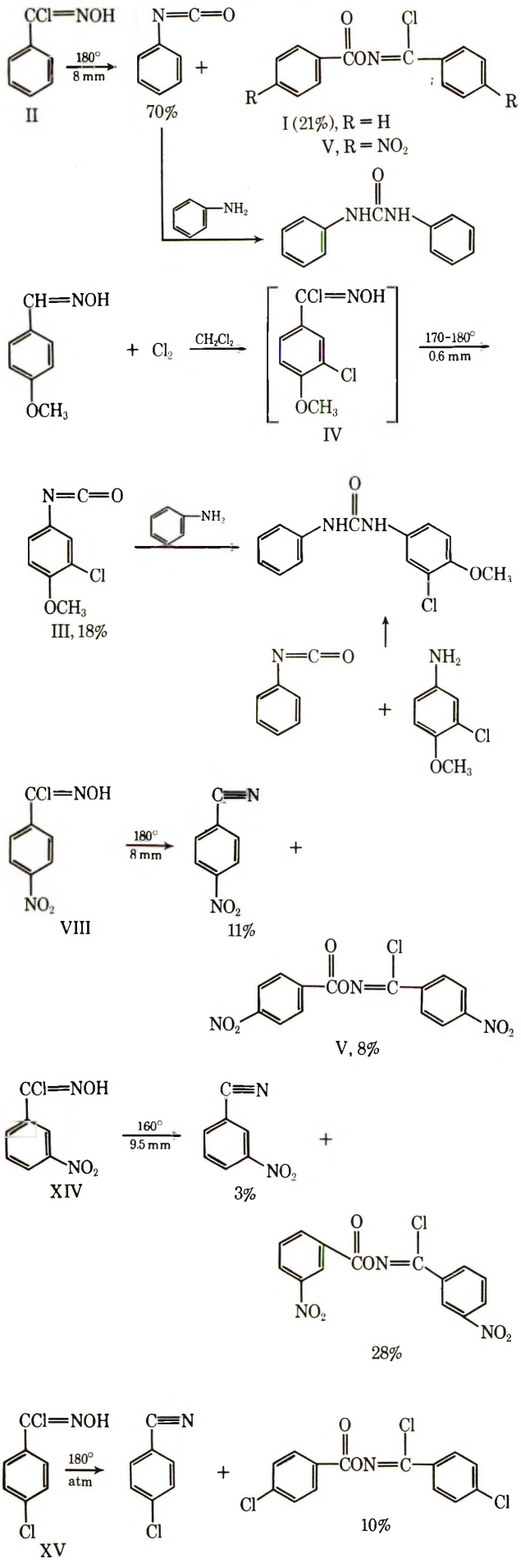
(1) See part I in this series: Y. H. Chiang, *J. Org. Chem.*, **36**, 2146 (1971).

SCHEME I



of benzoic acid (100%) is probably due to the partial hydrolysis of II. Compound II was identified by vpc from the comparison of retention time with an authentic sample. Compound V is identical with that obtained from the reaction of *p*-nitrobenzoyl chloride with *p*-nitrobenzhydroxamic chloride. This fact demonstrated that the pyrolytic product is indeed benzhydroxamic chloride *O*-ester. *p*-Nitro- and *m*-nitrobenzonitrile were isolated in 11 and 3%, respectively, from the reaction mixture. The identity of *p*-chlorobenzonitrile was only detected by ir (2220 cm^{-1}, $-C{\equiv}N$). Compound IV could not be isolated in pure form but its identity was verified by conversion to a urea derivative (Scheme I).

It was reported[2] that aromatic nitrile *N*-oxides sterically hindered by substituents of appropriate size in both ortho positions will not undergo the spontaneous dimerization to furoxans, generally characteristic of nitrile *N*-oxides. At temperatures above 100°, these nitrile oxides rearranged completely to the corresponding isocyanates. The possibility of nitrile *N*-oxide as a reaction intermediate in the formation of isocyanates *via* pyrolysis is excluded since no furoxan was isolated from the pyrolytic product. Furthermore, it is well known that benzonitrile *N*-oxide dimerizes rapidly at elevated temperatures.[2] It is interesting to note that the presence of an electron-withdrawing group or electron-donating group in the benzene ring lead to entirely different reaction products (Scheme I). On the other hand, the unsubstituted phenyl derivative took an intermediate course which yielded both phenyl isocyanate and I as the final products. The mechanism of this pyrolytic reaction was proposed on the basis of products isolated and substituent effects. The reaction pathways are formulated in Scheme II. An imidyl radical, *i.e.*, VI, was proposed as a reaction intermediate for isocyanate formation. Reactions which apparently involve the intermediacy of imidyl radicals are the introduction of cyano groups into hydrocarbons by by reaction with cyanogen chloride,[3,4] thermal cleavage reactions of *N*-chloroketimines,[5] and the photochemical reaction of unsaturated nitrogen-containing compounds.[6] In the cases of II and IV, an imidyl radical was formed upon pyrolysis which either underwent β scission (benzonitrile formation, path a) or rearranged to give phenyl isocyanate (path b).

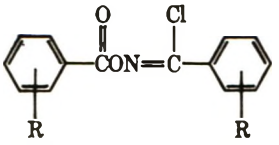
In the cases of nitro- or chloro-substituted benzhydroxamic chloride derivatives, a benzyl radical VII was proposed as an intermediate in the pyrolytic process. The salient facts associated with the postulated radical intermediate VII that eliminated a common imidyl radical intermediate for both reactions (Scheme II) are as follows: (1) the homolysis of VIII should occur in such a way as to provide the more stable transient free radical VII, which stabilized by the presence of the nitro group in the para position;[7] (2) the absence of *p*-nitrophenyl group migration in the course of reaction.

It has been shown that the decomposition of the

(2) (a) C. Grundmann and S. K. Datta, *J. Org. Chem.*, **34**, 2016 (1969); (b) C. Grundmann, H. D. Frommeld, K. Flory, and S. K. Datta, *ibid.*, **33**, 1464 (1968), and references cited therein.
(3) E. Muller and H. Huber, *Chem. Ber.*, **96**, 670, 2319 (1963).
(4) D. D. Tanner and N. J. Bunce, *J. Amer. Chem. Soc.*, **91**, 3028 (1969).
(5) M. L. Poutsma and P. A. Ibarbia, *J. Org. Chem.*, **34**, 2848 (1969).
(6) R. W. Binkley, *ibid.*, **34**, 2072 (1969).
(7) P. D. Bartlett and J. D. Cotman, *J. Amer. Chem. Soc.*, **72**, 3095 (1950).

TABLE I

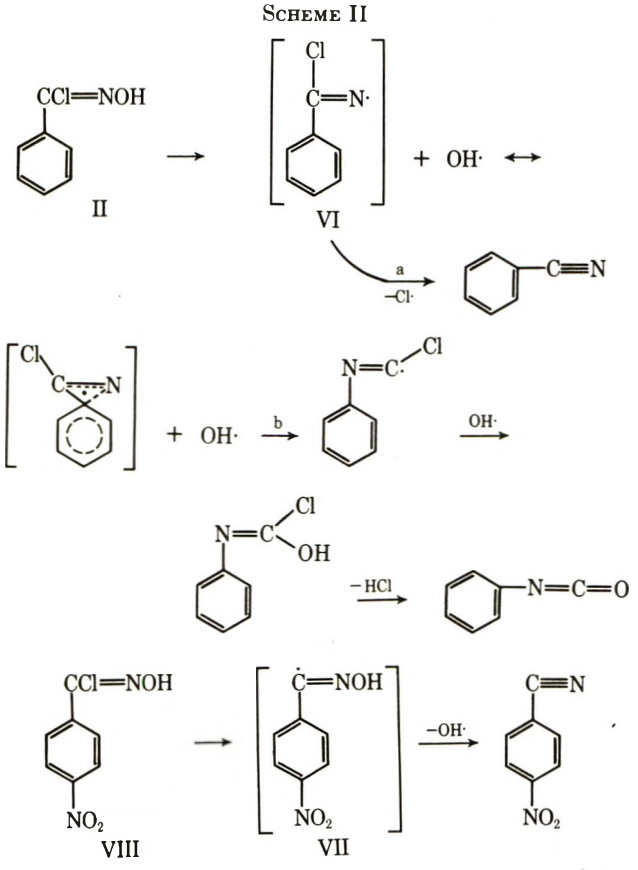
PHYSICAL PROPERTIES OF THE SUBSTITUTED *O*-BENZOYLBENZHYDROXAMIC CHLORIDE DERIVATIVES

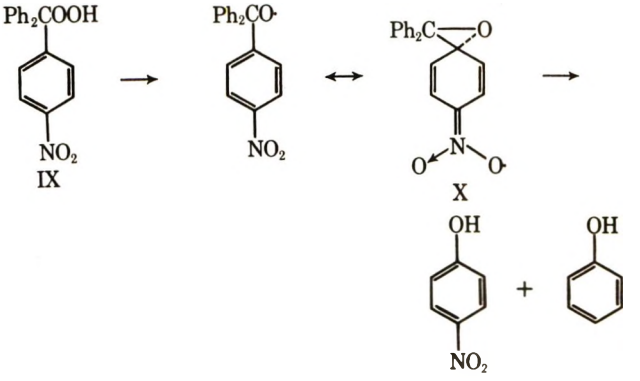


R	Registry no.	% yield	Mp, °C	Formula	Calcd, % C	H	N	Cl	Found, % C	H	N	Cl	λmax, mμ (ε); ν, cm⁻¹
H	29577-09-1	21	108–109[a]	$C_{14}H_{10}ClNO_2$	64.75	3.88	5.39	13.66	64.58	3.88	5.20	13.99	260 (25,700); 1760
m-NO_2	29577-10-4	28	191–192	$C_{14}H_8ClN_3O_6$	48.08	2.30	12.02	10.14	48.44	2.35	12.09	10.50	1775
p-NO_2	29577-11-5	8	202–203	$C_{14}H_8ClN_3O_6$	48.08	2.30	12.02	10.14	48.38	2.38	11.75	11.04	270 (27,900); 1775
p-Cl	29718-39-6	9.4	147–148.5	$C_{14}H_8Cl_3NO_2$	51.17	2.45	4.26	32.37	51.41	2.51	4.18	32.28	1770

[a] See ref 12.

SCHEME II





nitro-substituted peroxide IX in benzene yields over three times as much *p*-nitrophenol (resulting from migration of the *p*-nitrophenyl group) as phenol (resulting from phenyl migration).[7] This suggested that the migratory aptitude of a substituted aryl group is related to the effectiveness of the substituent in stabilizing the bridged transition state (or the bridged intermediate) in the rearrangement. As shown, the *p*-nitro group X would be expected to stabilize such a bridged radical by aiding in the delocalization of the unpaired electron. On the other hand, the apparent absence of *p*-nitrophenyl group migration could possibly be due to much higher rates of β elimination from the imidyl radical or instability of *p*-nitrobenzonitrile under the reaction conditions (*e.g.*, radical addition reactions). Further evidence is required to distinguish the exact nature of this reaction. The presence of nitrile derivatives and pyrolysis at low pressure (*ca.* 8 mm), which eliminated the hydrochloric acid if formed, excluded a Beckman-like ionic mechanism. These facts strongly supported the proposed free-radical mechanism.

The formation of I and its analogs is rationalized in Scheme III. Upon pyrolysis of substituted benzhydroxamic chlorides XVI, a nitrile derivative was obtained which in turn formed an adduct XVII *via* a cyclic mechanism. The formation of isoxazoline derivatives by refluxing II and its derivatives in toluene was reported by several authors.[8] Attention is called to the addition of oximes to α,β-unsaturated ketones.[9] It appears that the oximes, as 1,3 dipoles, react through their nitronic tautomeric form. The cyclic mechanism was proposed on this basis. Hydrolysis of XVII gave the final product. Compound XVII could not be isolated since hydrolysis occurred in the course of recrystallization (aqueous ethanol). The generation of iminoxy radicals from oximes with an oxidizing agent was reported by several authors.[10,11] It was reported[11] that thermal decomposition of *N*-benzhydryl-α,α-diaryl nitrones generated an iminoxy radical and a benzhydryl radical. The possibility that XVI is converted to an iminoxy radical XVIII followed by free-radical addition to the nitrile group cannot be excluded (Scheme III).

In conclusion, it was found that pyrolysis of XVI involved two reaction intermediates depending on the

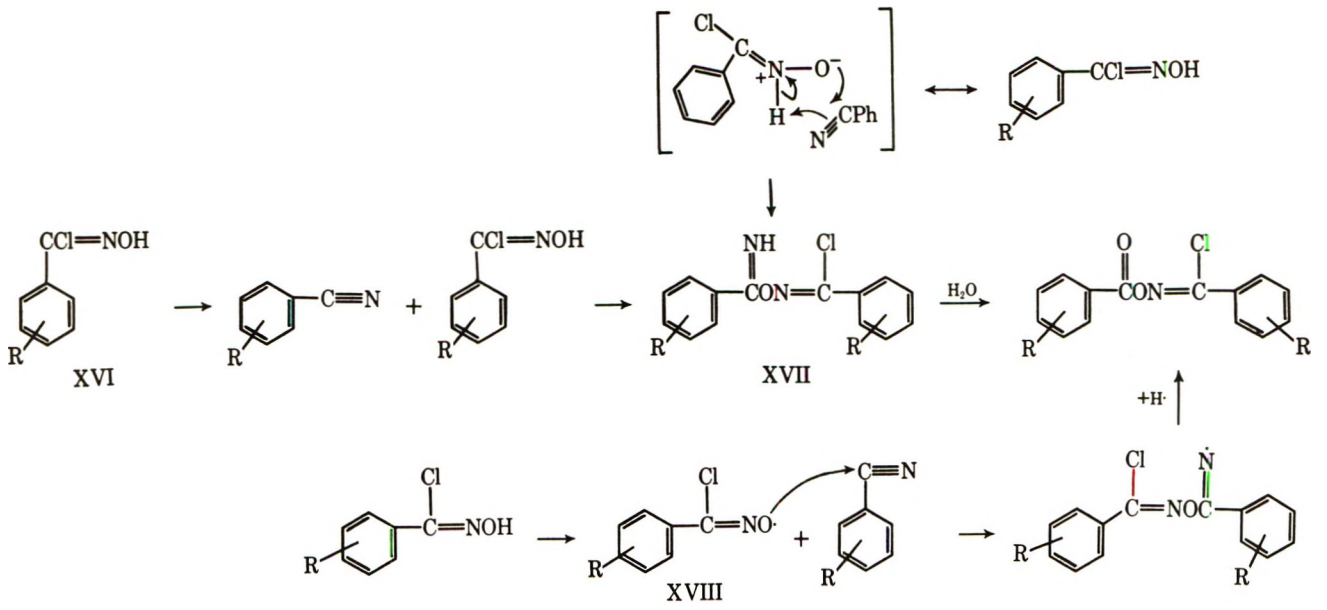
(8) (a) R. Lenaers and F. Eloy, *Helv. Chim. Acta*, **46**, 1067 (1963); (b) P. Vita Finzi and M. Arbasino, *Ric. Sci., Parte 2, R. Sez. A*, **8**, 1484 (1965); Chem. Abstr., **65**, 7162d (1966); (c) S. Morrocchi and A. Ricca, *Chim. Ind. (Milan)*, **49**, 629 (1967); *Chem. Abstr.*, **67**, 90737*f* (1967).

(9) A. Lablache-Combier and M. L. Villaume, *Tetrahedron*, **24**, 695 (1968).

(10) (a) M. Fedtke and H. Mitternacht, *Z. Chem.*, **4**, 389 (1964); *Chem. Abstr.*, **62**, 1533*f* (1965); (b) A. Caragheorgheopol, M. Hartmann, R. Kaehmstedt, and V. E Sahini, *Tetrahedron Lett.*, 4161 (1961).

(11) E. J. Grubbs, J. A. Villarreal, J. D. McCullough, Jr., and J. S. Vincent, *J. Amer. Chem. Soc.*, **89**, 2234 (1967), and references cited therein.

SCHEME III



substituent on a given aromatic ring. The rearrangement of II and IV to give isocyanate derivatives in combination with the isolation of nitrile derivatives from the reaction mixture strongly supported these facts. A four-centered mechanism was proposed for the formation of I and its analogs. It has been pointed out that the iminoxy radical addition mechanism cannot be excluded as an alternate pathway for the formation of I.

Experimental Section

The melting points were obtained on a Fisher-Jones melting point apparatus and are uncorrected, as are the boiling points. Ir spectra were recorded on a Perkin-Elmer Infracord Model 137 sodium chloride spectrophotometer. Uv spectra were obtained on a Coleman-Hitachi 124 double beam spectrophotometer in absolute ethanol. Mass spectra were taken on a Hitachi Perkin-Elmer RMV-7 mass spectrometer using an all-glass inlet. The microanalysis of the compounds were performed by Geller Microanalytical Laboratories, Saddle River, N. J. 07458.

Pyrolysis of Benzhydroxamic Chloride Derivatives XVI.—Typical procedures for the pyrolysis of II and its analogs are described. Most of the pyrolyses could be performed by the method used for II except XV. *When the thermolysis of XV was carried out under low pressure (ca. 10 mm, 180°), a violent explosion occurred.* The pyrolysis of XV must be carried under atmospheric pressure in thick-walled test tube.

Pyrolysis of Benzhydroxamic Chloride (II).—In a 10-ml round-bottomed flask fitted with a vacuum distillation setup is placed 2.57 g of II. After evacuation to a pressure of about 13 mm, the flask was heated in an oil bath (180°) for 30 min. Phenyl isocyanate [bp 104–105° (13 mm), 0.52 g (70%)] distilled off slowly. When the solid residue was crystallized from aqueous ethanol, 0.44 g (21%) of I, mp 108–109°, was obtained.[1] A small amount of the collected phenyl isocyanate was reacted with aniline in anhydrous ether giving *N,N*-diphenylurea. The mixture melting point with an authentic sample was not depressed.

Pyrolysis of 3-Chloro-4-methoxybenzhydroxamic Chloride (IV).—IV (4 g) was dissolved in 400 ml of methylene chloride at 0°. Chlorine gas was passed through this solution at a slow rate for 20 min. After the mixture stood in a cooling bath for 2 hr and then at room temperature overnight, air was bubbled through the reaction mixture until all the excess chlorine was removed. The solvent was removed under reduced pressure and the residue was vacuum distilled to give 0.86 g (18%), bp 140–143° (0.6 mm), of III. When a small amount of III was allowed to react with aniline, a urea derivative, mp 210–211°, was obtained. This compound proved to be identical with the urea obtained by the reaction of phenyl isocyanate with 3-chloro-4-methoxyaniline as shown by mixture melting point and ir spectrum.

Anal. Calcd for $C_{14}H_{13}ClN_2O_2$: C, 60.76; H, 4.73; N, 10.13; Cl, 12.81. Found: C, 60.96; H, 4.82; N, 10.08; Cl, 12.84.

Hydrolysis of I.—I (200 mg) was dissolved in an aqueous alcoholic sodium hydroxide solution (200 mg of sodium hydroxide in 20 ml of methanol and 10 ml of water) and stirred at room temperature overnight (*ca.* 18 hr). The solution was acidified with 5% hydrochloric acid and methanol was removed under reduced pressure. The aqueous solution was extracted with two 50-ml portions of ether and dried over anhydrous magnesium sulfate. After the ether solution was condensed, the residue was analyzed by vpc on an Aerograph Autoprep Model A-700 instrument using 10% Carbowax 20M on Anacrom ABS 70–80 mesh, 10 ft × 1/8 in. column. The ratio of benzoic acid/II is 4.57. When the residue was evaporated to dryness, a solid material was obtained. Upon crystallization of the solid, 97 mg (100%), mp 121–122°, of benzoic acid was collected.

Preparation of V.[12]—To an ether solution (150 ml) which contained 2.01 g (0.01 mol) of VIII and 1.41 g (0.01 mol) of *p*-nitrobenzoyl chloride was added 0.79 g (0.01 mol) of pyridine in 50 ml of ether at 0°. The reaction mixture was stirred at 0° for 1–2 hr and then left at room temperature overnight. After it was washed with 30 ml of water, the ether solution was dried and evaporated. The residue was crystallized from acetone, yielding 0.37 g of V, mp 203–204°. No melting point depression was observed when mixed with the pyrolysis product.

Acknowledgment.—The author is grateful to Dr. Victor Hansen for helpful discussion throughout this work. Thanks are also due to Dr. A. K. Bose for the measurements of nmr and mass spectra.

(12) *Beilstein*, 2nd ed, **9**, 214 (1956).

The Use of Lewis Base–Sulfur Trioxide Complexes as Reagents for the Beckmann Rearrangement of Ketoximes

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Complexes of sulfur trioxide with various Lewis bases have been studied as reagents for the Beckmann rearrangement of ketoximes. All the complexes studied yield isolable Beckmann intermediates, some of which have been identified. Only some of these intermediates could be hydrolyzed to the corresponding amides, but all of them yield their amides on pyrolysis. The intermediates most commonly found included the sulfonic acid derivative of the ketoxime which contained the Lewis base as an integral part of the intermediate. However, when the dimethylformamide–sulfur trioxide complex and the dioxane (di)–sulfur trioxide complex were used, two and three intermediates for the respective complexes were found.

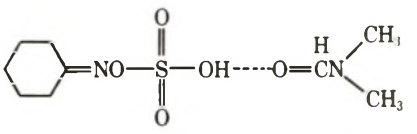
While sulfur trioxide has been reported to promote the Beckmann rearrangement, in all but a few special cases[1] the reactivity of free sulfur trioxide is too great to permit a controlled reaction. In the cases where this reaction was apparently possible,[2] no mention or observation was made to substantiate any formation of the corresponding N-substituted amide. The reaction between a ketoxime and several sulfur trioxide complexes has been reported[3,4] in limited studies in the past.

Results and Discussion

The Lewis bases studied as complexing agents for sulfur trioxide were *N*,*N*-dimethylformamide (DMF), *N*,*N*-diethylformamide, *N*-methylacetamide, *N*,*N*-dimethylacetamide, *N*,*N*-diethylacetamide, *N*-methylpropionamide, *N*,*N*-dimethylpropionamide, *N*,*N*-diethylpropionamide, *N*,*N*-dimethylbutyramide, *N*,*N*-diethylbutyramide, caprolactam, pyrrolidone, and *N*,*N*-dimethylbenzamide. It should be noted that any amide employed must be at least *N*-monoalkyl substituted to avoid dehydration to the nitrile. In addition to the above amides, various amines, cyclic ethers, nitriles, and nitro compounds were employed for this purpose. These were pyridine, 1,4-dioxane, tetrahydrofuran, benzonitrile, and nitrobenzene. Sulfur trioxide complexes of various polymers were also evaluated and include Carbowax 20M, polyvinyl pyrrolidone, trioxane, 2-vinylpyridine, nylon-6, and nylon-66.

The yields of caprolactam using the above complexes of sulfur trioxide were all in the range of 95–100%, with the exception of the amine complexes which were 0–30%. It was observed that in the case of the amine complexes the yield is inversely proportional to the basic strength of the amine employed.

To avoid the complexities associated with the rearrangement of a mixture of cis and trans oxime isomers, cyclohexanone oxime was chosen to evaluate the various sulfur trioxide complexes. During the course of the rearrangement of cyclohexanone oxime with these complexes, it was possible in all cases to isolate the corresponding intermediate. With the exception of three solid intermediates isolated while employing the dioxane complex, all other intermediates were oils of varying viscosity and stability. The dimethylformamide–sulfur trioxide is capable of forming two intermediates with cyclohexanone oxime on a one-to-one and two-to-one molar ratio of oxime to complex. This is the only complex examined that was capable of rearranging an oxime on greater than a one-to-one molar basis. Both intermediates were examined by nuclear magnetic resonance and infrared spectroscopy. However, the structural difference was difficult to elucidate because of their limited solubility. It was determined that the intermediate resulting from the one-to-one molar reaction is a hydrogen-bonded species of the sulfonic acid derivative of cyclohexanone oxime and dimethyl formamide as shown in (1). The nuclear magnetic



(1)

resonance data also suggest that a rapid equilibrium exists between the sulfonic acid and oxime portions of the intermediate.

Under normal conditions, the acidic rearranging reagent is neutralized and/or the intermediate is hydrolyzed prior to work-up of the reaction mixture. However, the hydrolysis of these intermediates under basic conditions can proceed in one of two directions, depending in part on the sulfur trioxide complex used. The hydrolysis reaction can produce caprolactam or the intermediate may simply revert to the free oxime, sulfate salt, and the Lewis base used in the complex. Cyclohexanone oxime intermediates can be hydrolyzed to caprolactam if the following Lewis bases are employed in the complex: 1,4-dioxane, tetrahydrofuran, caprolactam, *N*,*N*-diethylacetamide, *N*,*N*-diethylpropionamide, *N*,*N*-dimethylbutyramide, *N*,*N*-diethylbutyramide, and *N*,*N*-dimethylbenzamide. The rest of the intermediates listed previously revert to cyclohexanone oxime on hydrolysis.

An examination of the amides in Table I indicates that the degree of substitution on the nitrogen affects the route taken during hydrolysis when cyclohexanone oxime is used.

This is observed on comparing group Ia, Ib, and Ic, and group Id, Ie, and If. However, the results obtained using *N*,*N*-diethylformamide (Ig), and compared to those found for Ic and If, indicate that the degree of nitrogen substitution is not the only factor affecting the

(1) Potts (to Henkel and Cie GmbH), British Patent 732,899 (1955); N. Tokura, R. Asami, and R. Tado, *Sci. Rep. Res. Inst. Tohoku Univ., Ser. A*, **8**, 149 (1956).

(2) S. I. Burmestrov and A. G. Taranenko, *Ukr. Khim. Zh.*, **22**, 620 (1956); A. P. Terent'ev and N. B. Kupletskaya, *Zh. Obshch. Khim.*, **26**, 451 (1956).

(3) A. F. Turbak, *Ind. Eng. Chem., Prod. Res. Develop.*, **7**, 189 (1968).

(4) F. R. Atherton, A. L. Morrison, R. J. W. Cremyler, G. W. Kenner, A. Todd, and R. F. Webb, *Chem. Ind. (London)*, 1183 (1955).

TABLE I

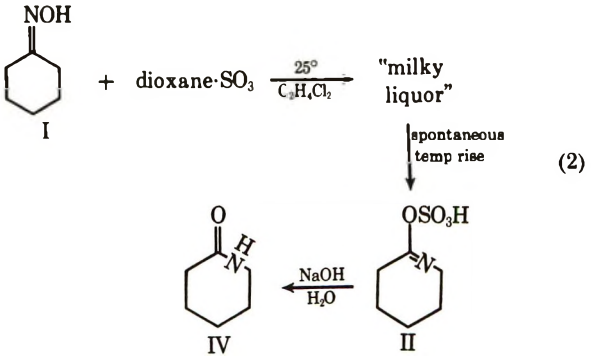
Lewis base used	No.	Hydrolysis product
$CH_3CONHCH_3$	Ia	Oxime
$CH_3CON(CH_3)_2$	Ib	Oxime
$CH_3CON(CH_2CH_3)_2$	Ic	Lactam
$CH_3CH_2CONHCH_3$	Id	Oxime
$CH_3CH_2CON(CH_3)_2$	Ie	Oxime
$CH_3CH_2CON(CH_2CH_3)_2$	If	Lactam
$HCON(CH_2CH_3)_2$	Ig	Oxime
$CH_3(CH_2)_2CON(CH_3)_2$	Ih	Lactam
$CH_2(CH_2)_2CONH$	Ii	Oxime
$CH_2(CH_2)_3CONH$	Ij	Lactam

hydrolysis route. Therefore, it appears that the carbon number (and/or molecular weight) of the amide is the major factor influencing the hydrolysis route taken. This is substantiated by comparing Ie with Ih and Ii with Ij. This last sample in particular serves to indicate that the carbon number and not the parent chain length is responsible for the preferred route taken during hydrolysis. Therefore, it can be generalized that the cyclohexanone oxime intermediates formed from amide complexes containing five carbons or less will revert back to the oxime, while those intermediates formed from amide complexes containing six carbons or more will proceed on to the lactam upon hydrolysis. This generalization may not hold true when other oximes are used.

The structure of the oxime also plays an important role in the hydrolysis. The intermediate from the reaction of cyclohexanone oxime and the dimethylformamide–sulfur trioxide complex reverts to free oxime upon hydrolysis while 2-*n*-butylcyclohexanone oxime and 2-methylcyclohexanone oxime react with the same complex to form intermediates which hydrolyze to their respective lactams, the latter being a mixture.

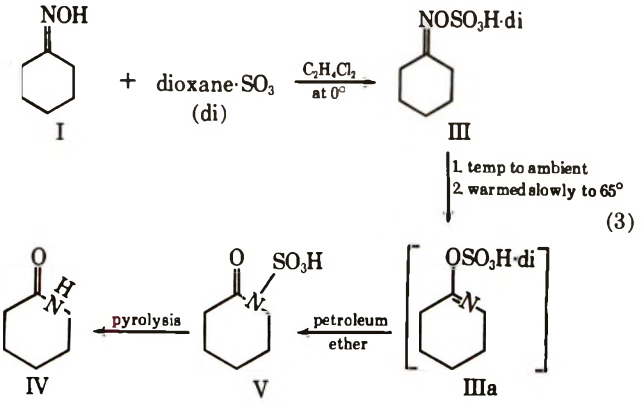
A number of solvent types can be employed to prepare these Beckmann intermediates. They include alcohols, ethers, esters, amines, ketones, amides, paraffins, and halogenated hydrocarbons. Although specific members of each broad classification have served with varying degrees of success, it was found that the halogenated hydrocarbons are the most suitable for this purpose. The reaction between any oxime and sulfur trioxide complex is nearly instantaneous and complete in these solvents. An exception to this was observed with the amine complexes. The amines form a very stable complex with sulfur trioxide due to their relatively high basic strength. This results in a very low reactivity and produces low yields of amides.

Although only approximately one-half of the cyclohexanone oxime intermediates studied could be hydrolyzed to the amide, it was possible to pyrolyze all of them to the amide. The pyrolysis is highly exothermic. It can be initiated by rapidly raising the temperature of the intermediate to its decomposition point after which the heat of reaction allows it to continue. Once initiated, this reaction is essentially spontaneous so that it becomes necessary to provide sufficient cooling to keep the reaction under control. The pyrolysis can be conducted in the gas phase in the presence of the solvent or in a small batch-type reaction after the solvent has been removed. The pyrolysis of these intermediates will not produce good yields of amide if initiated under super- or subatmospheric pressures. Although a decomposition does occur under these conditions, the reaction product contains neither caprolactam, cyclohexanone oxime, nor any Beckmann intermediate. The products from such a decomposition have not been identified. The reaction of cyclohexanone oxime with the dioxane–sulfur trioxide (di-SO_3) complex yields solid intermediates which more readily lend themselves to structural analysis. This reaction has been reported[3] and a mechanism was formulated according to eq 2.



(2)

However, by slightly varying the reaction conditions, a more complete picture of the reaction sequence was observed. On lowering the temperature at which the reaction was run by only a few degrees, a series of different intermediates was found as shown in eq 3.



(3)

The first intermediate (III) has a melting point of 26° dec[5] and remains as a white solid in the reaction solvent below 10°. Allowing the reaction mixture to come to ambient temperature results in the solution of III, but the "milky liquor" or a spontaneous temperature rise was not observed as reported by Turbak.[3] This indicates that the intermediates initially formed in eq 2 and 3 are not the same. When III is warmed to 65°, it is spontaneously transformed to a second intermediate (V) exothermically. Possibly this intermediate is derived by the Chapman rearrangement of IIIa with the loss of dioxane.

Experimental Section

Gas chromatographic analyses of the reaction products were performed on an F & M Model 720 dual column chromatograph equipped with thermal conductivity detectors. The column used was 0.25 in. × 4 ft stainless steel packed with 25% SE-31, with

(5) Although it is possible to isolate this intermediate, *extreme care* should be taken since experience has shown that it can decompose explosively.

a helium flow of 50 ml/min. Analyses were made at 135° isothermally with a bridge current of 150 mA.

Preparation of Sulfur Trioxide Complexes.—The method of preparation of all the complexes employed in this study is essentially identical. In general, the Lewis base is dissolved (suspended if an insoluble polymer) in dichloromethane, cooled to ice bath temperature, and 1 molar equiv of sulfur trioxide was added. The white crystalline complex precipitates, is filtered, and washed with dichloromethane. The melting point of these complexes is difficult to determine because of their rapid uptake of water. Two examples illustrate this preparation.

Dimethylformamide–Sulfur Trioxide Complex.—Dimethylformamide (100 g, 1.37 mol) in 75 ml of dichloromethane was placed in a 500-ml three-necked round-bottom flask equipped with a magnetic stirrer, cold finger condenser, and drying tube. This solution was cooled to 0° in an ice water bath and 1.37 mol (109 g, 56 ml) of stabilized liquid sulfur trioxide (at room temperature) was added dropwise from a pressure equalizing dropping funnel over a period of 45 min. Upon completion of addition, the white crystalline complex was removed by vacuum filtration and washed several times with dichloromethane. During filtration and washing, the filtering funnel was covered with a rubber membrane to prevent exposure of the complex to atmospheric moisture. A theoretical quantity (209 g) of the complex was obtained.

Polyvinyl Pyrrolidone.—Liquid sulfur trioxide (0.5 g) was added dropwise to a previously cooled solution of 1 g of polyvinyl pyrrolidone in 30 ml of 1,2-dichloroethane. The white crystalline complex began to precipitate from solution soon after the initial addition of the sulfur trioxide. After the required volume of sulfur trioxide had been added, the solid was removed by vacuum filtration, washed with 1,2-dichloroethane, and vacuum dried at room temperature to give a 98% yield (1.5 g) of the complex. Titration of a small quantity of this complex showed the available sulfur trioxide concentration to be 0.0046 mol/g of complex.

Beckmann Rearrangement Studies. Rearrangement of Cyclohexanone Oxime Using Flow-through Reactor.—A 1 × 14 cm condenser was clamped in a vertical position and packed with 2.7 g (0.018 mol) of the dimethylformamide–sulfur trioxide complex supported on a glass wool plug. Water at 40° was circulated through the condenser jacket. Cyclohexanone oxime (2.0 g, 0.018 mol) was dissolved in 5.0 ml of dichloromethane contained in a small pressure-regulating dropping funnel. This solution was then allowed to flow through the reagent bed under a slight pressure to prevent the solvent from boiling. As the reaction proceeded, the reagent was consumed and the effluent from the column was collected in a two-necked 50-ml round-bottom flask. The condenser was washed with 2.0 ml of dichloromethane and the washings were added to the reaction mixture. The solvent was removed by evacuating the flask on a rotatory evaporator at 3 mm at room temperature over a 0.5-hr period. The clear viscous oil remaining in the flask is the Beckmann intermediate. An electric resistance heater was immersed in the oily intermediate. With the material previously cooled to 0°, the resistance heater was activated momentarily to initiate the decomposition, after which the reaction proceeded on its own due to the exothermicity of the reaction. Immediately after the onset of the pyrolytic reaction, the pressure was rapidly lowered to 3 mm to remove liberated sulfur trioxide. The pyrolysis product (greenish brown oil) was taken up in methanol. A thin layer chromatogram (2% methanol in benzene on silica gel) confirmed the presence of free caprolactam. Examination of this solution by glc showed a 96% yield of caprolactam based on molar response.

Vapor Phase Pyrolysis of Beckmann Intermediate.—A one-to-one molar ratio intermediate was prepared using the flow-through reactor technique. The total reaction mixture was drawn into a 10-ml glass syringe equipped with a 5.5 in. filling needle. The syringe was mounted horizontally in an adjustable rate infusion pump. The needle was completely inserted through a rubber septum into the horizontal pyrolysis tube (1 × 47 cm), containing a helium flow of 100 ml/min and equipped with a cold trap, so that the tip of the needle just touched the edge of a glass wool packing 5 cm in length. The tube packing was centered in a micro combustion furnace 20 cm in length. With the furnace preheated to 230 ± 2°, the intermediate reaction mixture was injected at the rate of 0.2 ml/min. After complete injection, the furnace was rapidly cooled using compressed air and the syringe needle withdrawn. The residual material in the heated zone was eluted using methanol and combined with the condensate in the cold trap. This mixture was neutralized with ammonia and filtered, and the filtrate made up to 250.0 ml with methanol. Examination of this solution by glc showed a 67.5% yield of caprolactam based on molar response.

Dioxane–Sulfur Trioxide Intermediates.—The dioxane–sulfur trioxide complex (3.0 g, 0.018 mol) was slurried in 10 ml of 1,2-dichloroethane using a magnetic stirrer and cooled to 0° using an ice water bath. An equimolar quantity of cyclohexanone oxime (2.0 g) was placed in a pressure-equalizing dropping funnel and dissolved in 10 ml of dichloroethane. This solution was added slowly to the slurry of the complex over a 15-min period in order to maintain the reaction temperature at 0°. After the addition was complete, the white crystalline intermediate III was removed by vacuum filtration under anhydrous conditions. Examination of this intermediate by ir showed a sulfate group (1240 cm^{-1}) present with no carbonyl evident (1669 cm^{-1}). Nmr showed that a seven-membered lactam ring was not present by the absence of the δ 3.4 peak (CH_2NCO) and that dioxane was present in a one-to-one molar ratio to the cyclohexane portion of the intermediate. The experimentally determined molecular weight and elemental analysis also support the proposed structure. The molecular weight was determined by a vapor pressure osmometer method to give 290 *vs.* 281 calculated. *Anal.* Calcd for $C_{10}H_{19}O_6NS$: C, 42.7; H, 6.8; N, 5.0; O, 34.1; S, 11.4. Found: C, 42.8; H, 6.7; N, 4.9; O, 34.3; S, 11.4.

When this intermediate, as formed in the reaction solvent, was slowly warmed to 65° using a water bath, it was spontaneously transformed to a second intermediate (V, eq 3) exothermally. Examination of this intermediate by ir showed a lactam carbonyl (1669 cm^{-1}). The nmr spectrum exhibited peaks (acetone-d_6 *vs.* TMS) at δ 13.8 (acid H), 3.4 (CH_2NCO), 2.3 (CH_2CON). No dioxane was evident and an electronegative group was present on the nitrogen. *Anal.* Calcd for $C_6H_{11}O_4NS$: C, 37.3; H, 5.7; N, 7.3; O, 33.1; S, 16.6; mol wt, 193. Found: C, 37.4; H, 5.8; N, 7.2; O, 33.2; S, 16.6; mol wt, 188.

Registry No.—DMF–SO_3 complex, 29584-42-7; *N,N*-diethylformamide–SO_3 complex, 29584-43-8; *N*-methylacetamide–SO_3 complex, 29584-44-9; *N,N*-dimethylacetamide–SO_3 complex, 29641-83-6; *N,N*-diethylacetamide–SO_3 complex, 29584-45-0; *N*-methylpropionamide–SO_3 complex, 29584-46-1; *N,N*-dimethylpropionamide–SO_3 complex, 29641-84-7; *N,N*-diethylpropionamide–SO_3 complex, 29584-47-2; *N,N*-dimethylbutyramide–SO_3 complex, 29584-48-3; *N,N*-diethylbutyramide–SO_3 complex, 29584-49-4; caprolactam–SO_3 complex, 29641-85-8; pyrrolidone–SO_3 complex, 29584-50-7; *N,N*-dimethylbenzamide–SO_3 complex, 29584-51-8.

Peroxide. X. A Mild and General Synthesis of Peroxy Acids[1]

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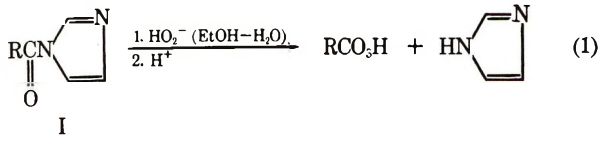
Peroxy acids are prepared in high yields by perhydrolysis of acyl diethyl phosphates in ethyl ether solution. The reaction is weakly catalyzed at low concentrations of methanesulfonic acid (MSA) but proceeds rapidly using equimolar proportions of MSA and the mixed anhydride. The acyl diethyl phosphate intermediates are prepared in ether solution by acylation of silver diethyl phosphate. The method is particularly useful for preparing methoxy-substituted and sterically hindered peroxy acids.

Many peroxy acids may be prepared by judicious choice of the methods and modifications currently available for their synthesis.[2,3] Some of the methods are comparatively superior to others for specific preparations, but each is limited in scope, yields, or preparative convenience. For example, the direct reaction between carboxylic acids and hydrogen peroxide in methanesulfonic acid solution is advantageous for preparing many peroxy acids in nearly quantitative yields, but the procedure fails in its application to the preparation of methoxy-substituted peroxybenzoic acids.[1] The monomethoxy derivatives, illustrated by peroxyanisic, are obtained in low yields (~35%) by alkaline perhydrolysis of either the acyl chloride[4] or the diacyl peroxide.[5]

Recently, Folli and Iarossi[6] have reported a new, general method for the preparation of peroxy acids, under mild conditions, that utilizes the imidazolides of carboxylic acids (I) (eq 1). The peroxy acids are ob-

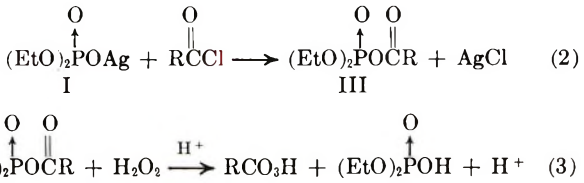


I (1)

tained in yields averaging 50% by perhydrolysis of I in alkaline media. This method represents an improvement over former procedures for preparing methoxy-substituted peroxy acids and provides an effective route to the optically active and sterically hindered types.

In the course of our investigations of the kinetics of epoxidation,[7] several new peroxy acids were desired but were unobtainable by conventional methods. Since the synthetic method of Folli and Iarossi had not been published in the early stages of this work, we devised a new synthesis that appears to be general. The method takes advantage of the facility of acyl phosphates to hydrolyze under mild acid catalysis.[8]

The procedure entails the preparation of acyl diethyl phosphates (III) by acylation of silver diethyl phosphate (II) in ether solution (eq 2) and acid-catalyzed perhydrolysis of the mixed anhydride III to peroxy acid and diethyl hydrogen phosphate (eq 3). Although



the silver salt is slightly soluble in ether, acylation proceeds instantaneously with the solid phase as well as in solution.

The conditions and yields for preparing various peroxy acids are recorded in Table I. The acid concentrations affecting the conversion of several mixed anhydrides to peroxy acids (Table II) were determined as a guide for formulating the preparative conditions listed in Table I. The method provides a conveniently useful and mild route to the preparations of methoxy-substituted and sterically hindered peroxy acids as well as others normally obtained with difficulty. The yields based on conversion of acid chloride average 75%.

TABLE I

PREPARATIVE CONDITIONS AND YIELDS OF PEROXY ACIDS

Acyl diethyl phosphate[a]	Mole ratio of H_2O_2:ADP:MSA[b]	Temp, °C	Time, hr	% peroxy acid[c]	Yield, %[d]
p-Methoxybenzoyl	10:2:1	10–15	1	89	82
	5:1:1	15	1	91	86
3,4,5-Trimethoxybenzoyl	5:1:1	15	1	88	63
2,4,6-Trimethylbenzoyl	5:1:0[e]	0–5	0.5	80	74
o-Nitrobenzoyl	5:1:2	25–30	1.5	74	74
p-Nitrobenzoyl	5:1:2	25–30	1.5	87	74
Stearoyl	5:1:1	25–30	1	92	74
Cinnamoyl	5:1:1	20	1.5	91	74
Pivaloyl	5:1:1	15	1	98	84

[a] Refer to Experimental Section for yields (based on acyl chlorides) and physical data of acyl diethyl phosphates. [b] ADP, acyl diethyl phosphate; MSA, methanesulfonic acid; H_2O_2, 98% concentration; reaction conducted in ethyl ether. [c] Based on iodometric analysis of crude product (see ref 15 for method used). [d] Yield of crude product based on acid chloride. [e] Reaction proceeds in the absence of MSA.

The disadvantage of the extra step for converting carboxylic acids to acyl chlorides is offset by the high yields of product. Folli and Iarossi[6] stressed the sensitivity of some types of carboxylic acids such as α or β optically active acids to the effects of strong acid environments as another disadvantage in the use of acyl chloride procedures. Examples of carboxylic acids

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TABLE II

VARIATION IN CONDITIONS FOR CONVERSIONS OF ACYL DIETHYL PHOSPHATES TO PEROXY ACIDS[a,b]

Acyl in ADP[c]	H_2O_2 concn (of soln), %	MSA/ ADP[c,d] mole ratio	Time, hr	Peroxy acid, % formed
p-Methoxybenzoyl	65	1	3	28
	65	2	4	46
	98	0.2	2.5	38
	98	0.5	0.5	56
	98	0.5	1	71
	98	0.5	2	80
	98	1	0.5	88
	98	1	1	91
	98	1	1.5	89
2,4,6-Trimethyl-benzoyl	98	0[e]	0.5	22
	98	0[e]	1	47
	98	0[e]	1.5	60
	98	0[e]	2	64
p-Nitrobenzoyl	98	1	2	0
	98	2	2	~1
	98	2	2 (25°)	11

[a] Solutions (1 *M*) in ethyl ether. [b] Reactions at 15° except where indicated. [c] ADP, acyl diethy lphosphate; MSA, methanesulfonic acid. [d] H_2O_2:ADP, 5:1 (mole ratio). [e] Perhydrolysis in absence of MSA.

from this class were not examined in the present work, but their conversion to acyl chlorides with retention of optical purity may be expected in view of the recently improved gentle techniques for conducting acyl chloride synthesis using dimethylformamide catalysis at low temperatures[9] or in the neutral environment of the triphenylphosphine–carbon tetrachloride reaction.[10]

Although the limited data of Tables I and II are inadequate for a mechanistic interpretation of the acid-catalyzed perhydrolysis of acyl diethyl phosphates, they suggest rate effects by substituents in the benzoyl moiety similar to those reported for the related hydrolysis of acyl phosphates RC(=O)P(→O)$(OH)_2$.[11] A comparison of the differences in preparative conditions and yields of peroxy acids obtained from *p*-methoxybenzoyl and *p*-nitrobenzoyl diethyl phosphates (Tables I and II) suggests that the perhydrolysis rate decreases as the electron-withdrawing effect of the ring substituent increases. The ease of perhydrolysis of 2,4,6-trimethylbenzoyl diethyl phosphate, in the absence of acid catalysis, indicates that reaction may proceed *via* an acylium ion intermediate, since the steric compression of the two ortho methyl groups and the electron donation of the para methyl group would disfavor a bimolecular reaction.[12]

Experimental Section

Materials.—Hydrogen peroxide (98 and 65% concentrations) was obtained from Food Machinery and Chemical Corp. *Olefin-free* petroleum ether (bp 30–40°) was obtained by sulfuric acid treatment and distillation.

Diethyl Phosphate.—The reagent was prepared by the method of Toy.[13] (Note that the presence of hydrogen chloride as an impurity in diethyl phosphorochloridate induces an uncontrollable exothermic reaction with formation of undesired products. This may be avoided by distilling diethyl phosphorochloridate before use.[14])

Silver Diethyl Phosphate.—The silver salt was prepared by reaction of diethyl phosphate (18.59 g, 0.12 mol) and silver carbonate (13.78 g, 0.05 mol) in ethyl ether (100 ml) at 25°. The stirred slurry was filtered after decantation from the more dense unreacted silver carbonate that settles to the bottom of the flask. The filtered silver salt was ether washed and dried *in vacuo* at 90°, yield 21.4 g (82%).

Anal. Calcd for $C_4H_{10}AgO_4P$: C, 18.41; H, 3.86; Ag, 41.34; P, 11.87. Found: C, 18.56; H, 3.97; Ag, 41.07; P, 11.96.

Preparation of Acyl Diethyl Phosphates.—The preparation described for anisoyl diethyl phosphate is typical of the class of acyl diethyl phosphates. Elemental analyses were obtained only on the solid mixed anhydrides which were easily purified by crystallization. For the peroxy acid preparations, the anhydrides were used as obtained without further purification.

Anisoyl Diethyl Phosphate.—Anisoyl chloride (8.50 g, 0.05 mol) was added dropwise to a stirred slurry of silver diethyl phosphate (19.6 g, 0.075 mol) in ethyl ether (100 ml). The ether solution was stirred for 1 hr at 25° and filtered to remove unreacted silver diethyl phosphate and silver chloride. Filtrates that appeared clouded by small amounts of suspended silver salts were easily clarified by filtration through a small quantity of Florisil. Evaporation gave a light yellow oil (13.5 g, 94% yield) having the appropriate ir absorptions for carbonyl at 1740 and broad phosphorus–oxygen peaks at 1260 and 1025 cm^{-1} [reported absorptions for organophosphorus compounds:[15] P=O (unbonded) at 1350–1250, P—O—C (aliphatic) at 1050–990 cm^{-1}]. The oil product was used without further purification.

Other Acyl Diethyl Phosphates.—The phosphate anhydrides listed in Table I were prepared as described for anisoyl diethyl phosphate using the following quantities of reactants and reaction conditions.

3,4,5-Trimethoxybenzoyl Diethyl Phosphate.—3,4,5-Trimethoxybenzoyl chloride (6.9 g, 0.03 mol) was added to silver diethyl phosphate (10.4 g, 0.04 mol) in ethyl ether (25 ml), yield 7.45 g (72%). The prouct was recrystallized from ethyl ether–petroleum ether (2:1, 10 ml) at −20°: mp 44–45°; ir C=O at 1740, P=O at 1270, P—O—C at 1025 cm^{-1}.

Anal. Calcd for $C_{14}H_{21}O_8P$: C, 48.28; H, 6.03; P, 8.91. Found: C, 48.44; H, 5.90; P. 8.82.

2,4,6-Trimethylbenzoyl Diethyl Phosphate.—2,4,6-Trimethylbenzoyl chloride (5.49 g, 0.03 mol) was added to silver diethyl phosphate (13.1 g, 0.05 mol) in ethyl ether (100 ml): yield 8.44 g (93%); ir C=O at 1758, P=O at 1290, P—O—C at, 1028 cm^{-1}.

***p*-Nitrobenzoyl Diethyl Phosphate.**—*p*-Nitrobenzoyl chloride (1.82 g, 0.01 mol) dissolved in ethyl ether (10 ml) was added to silver diethyl phosphate (4.12 g, 0.015 mol) in ethyl ether (25 ml). The product (3.0 g, 85% yield) recrystallized from ethyl ether–petroleum ether (1:1, 8 ml/g) to give a light yellow solid: mp 47–48°, ir C=O at 1740, P=O at 1280, P—O—C at 1030 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}NO_7P$: C, 43.57; H, 4.65; N, 4.62; P, 10.21. Found: C, 43.83; H, 4.75; N, 4.41; P, 10.26.

***o*-Nitrobenzoyl Diethyl Phosphate.**—*o*-Nitrobenzoyl chloride (5.75 g, 0.03 mol) dissolved in ethyl ether (25 ml) was added to silver diethyl phosphate (13.05 g, 0.05 mol), in ethyl ether (75 ml). The product (8.52 g, 95%) was a light yellow oil: ir C=O at 1752, P=O at 1280, P—O—C at 1025 cm^{-1}.

Stearoyl Diethyl Phosphate.—Stearoyl chloride (9.01 g, 0.03 mol) was added to silver diethyl phosphate (12.05 g, 0.05 mol) in ethyl ether (50 ml). The product (13 g, 100%) was purified by recrystallization from ethyl ether (2 ml/g) (note that if moisture is present some insoluble symmetrical stearic anhydride is formed): mp 36–37°; ir C=O at 1775, P=O at 1285, P—O—C at 1033 cm^{-1}.

Anal. Calcd for $C_{22}H_{45}O_5P$: C, 62.83; H, 10.78; P, 7.36. Found: C, 62.80; H, 10.85; P, 7.15.

Cinnamoyl Diethyl Phosphate.—Cinnamoyl chloride (5.00 g, 0.03 mol) dissolved in ethyl ether (25 ml) was added to silver diethyl phosphate (7.83 g, 0.03 mol) in ethyl ether (50 ml): yield of oil product 7.12 g (81%); ir C=O at 1735, P=O at 1270, P—O—C at 1030, C=C (aromatic conjugation) at 1628, HC=CH (trans) at 975 cm^{-1}.

Pivaloyl Diethyl Phosphate.—Pivaloyl chloride (3.62 g, 0.03 mol) dissolved in ethyl ether (5 ml) was added to silver diethyl

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phosphate (9.14 g, 0.035 mol) in ethyl ether (50 ml): yield of oil product 6.05 g (85%); ir C=O at 1760, P=O at 1283, P—O—C at 1020 cm^{-1}.

Preparation of Peroxy Acids. Peroxyanisic Acid.—Hydrogen peroxide (3.4 g of 98% concentration, 0.10 mol) was added dropwise to a mixture of anisoyl diethyl phosphate (5.76 g, 0.02 mol) and methanesulfonic acid (0.96 g, 0.01 mol) in ethyl ether (10 ml) at 10–15°. After complete addition of hydrogen peroxide, the mixture was stirred for 90 min at room temperature. Ice-cold water was added (10 ml) and the peroxy acid was extracted with chloroform. The chloroform solution was water washed, briefly dried with anhydrous sodium sulfate, and evaporated to give peroxyanisic acid (3.36 g, 87% peroxy acid content by iodometric analysis.[1,16] The product was purified by recrystallization from chloroform (8 ml/g of peroxy acid) at 0°, mp 87–88° (lit.[17] 85–86°).

Other Peroxy Acids.—The peroxy acids were prepared by the procedure described for peroxyanisic acid using the following quantities of reactants. The reaction conditions, yields, and peroxy acid content are recorded in Table I.

3,4,5-Trimethoxyperoxybenzoic Acid.—Methanesulfonic acid (0.96 g, 0.01 mol) and H_2O_2 (1.7 g, 0.05 mol) were added to 3,4,5-trimethoxybenzoyl diethyl phosphate (3.48 g, 0.01 mol) dissolved in ethyl ether (10 ml) at 15°. The product (2.03 g, 88% peroxy acid content) was recrystallized from chloroform–petroleum ether (2:1, 15 ml) at −20°, mp 84–85°.

2,4,6-Trimethylperoxybenzoic Acid.—Methanesulfonic acid was not required as a catalyst for this preparation. H_2O_2 (3.4 g, 0.10 mol) was added to 2,4,6-trimethylbenzoyl diethyl phosphate (6.0 g, 0.02 mol) in ether (3 ml) at 0–5° and the reaction was completed at 15°. The product solidified from solution in 20 min (3.5 g, 80% peroxy acid content) and was recrystallized from ethyl ether–petroleum ether (5:3, 16 ml) at −20°, mp 55.5–57°. (Note that this compound is sometimes difficult to isolate in pure form. A semisolid peroxy acid was obtained from one preparation that spontaneously decomposed to tar with evolution of heat. In the case of studies not requiring the solid peroxy acid, it may be preferable to use the dried chloroform solution directly.)

***p*-Nitroperoxybenzoic Acid.**—Methanesulfonic acid (0.67 g, 0.007 mol) and H_2O_2 (0.30 g, 0.075 mol) were added to a solution of *p*-nitrobenzoyl diethyl phosphate (1.0 g, 0.0035 mol) in ethyl ether (2 ml) at 25–30°. The product (0.85 g, 87% peroxy acid content) was recrystallized from chloroform (30 ml) at 0°, mp 138–139° (lit.[1] mp 138° dec).

***o*-Nitroperoxybenzoic Acid.**—Methanesulfonic acid (1.96 g, 0.02 mol) and H_2O_2 (1.70 g, 0.05 mol) were added to a solution of *o*-nitrobenzoyl diethyl phosphate (3.03 g, 0.01 mol) in ethyl ether (5 ml) at 25–30°. The product (1.5 g, 74% peroxy acid content) was recrystallized from chloroform–petroleum ether (1:1, 40 ml/g) at 0°, mp 97–98° (lit.[1] mp 95–96°).

Peroxystearic Acid.—Methanesulfonic acid (0.98 g, 0.01 mol) and H_2O_2 (1.7 g, 0.05 mol) were added to a solution of stearoyl diethyl phosphate (4.21 g, 0.01 mol) in ethyl ether (15 ml) at 20° and the reaction was completed at 25–30°. The product (2.98 g, 92% peroxy acid content) was recrystallized from petroleum ether (20 ml/g) at 0°, mp 66–67° (lit.[1] mp 65°).

Peroxycinnamic Acid.—Methanesulfonic acid (0.96 g, 0.01 mol) and H_2O_2 (1.70 g, 0.05 mol) were added to a solution of cinnamoyl diethyl phosphate (2.94 g, 0.01 mol) in ethyl ether (3 ml). The product (1.60 g, 91% peroxy acid content) was recrystallized from chloroform–petroleum ether (1:2, 30 ml/g) at −20°, mp 75–76.5°.

Peroxypivalic Acid.—Methanesulfonic acid (1.96 g, 0.02 mol) and H_2O_2 (3.40 g, 0.10 mol) were added to a solution of pivaloyl diethyl phosphate (5.76 g, 0.02 mol) in ethyl ether (5 ml). A slight modification for the isolation of this low molecular weight peroxy acid was preferred to the use of chloroform as extraction solvent by the addition of ice and saturated ammonium sulfate solution and several extractions with olefin-free petroleum ether. The combined extracts were washed twice with ammonium sulfate solution, dried over anhydrous sodium sulfate, filtered, and analyzed volumetrically. The oily product (2.42 g, 98%) was recovered by evaporation of solvent but was not further purified.

Registry No.—Silver diethyl phosphate, 29912-99-0; anisoyl diethyl phosphate, 29913-00-6; 3,4,5-trimethoxybenzoyl diethyl phosphate, 29913-01-7; 2,4,6-trimethylbenzoyl diethyl phosphate, 29936-58-1; *p*-nitrobenzoyl diethyl phosphate, 29913-02-8; *o*-nitrobenzoyl diethyl phosphate, 29913-03-9; stearoyl diethyl phosphate, 29843-36-5; cinnamoyl diethyl phosphate, 29920-14-7; pivaloyl diethyl phosphate, 7334-50-1; peroxyanisic acid, 29913-05-1; 3,4,5-trimethoxyperoxybenzoic acid, 29913-06-2; 2,4,6-trimethylperoxybenzoic acid, 19910-28-2; *p*-nitroperoxybenzoic acid, 943-39-5; *o*-nitroperoxybenzoic acid, 1711-41-7; peroxystearic acid, 5796-86-1; peroxycinnamic acid, 16667-07-5; peroxypivalic acid, 14909-78-5.

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The Reaction of Tolan with a Mixture of Iodine and Peracetic Acid[1]

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The reaction of tolan with a mixture of iodine and peracetic acid in acetic acid stereospecifically gave *trans*-α-iodo-α′-acetoxystilbene (IAS) together with benzil at 50° in the dark. IAS was oxidized by peracetic acid to form benzil much faster than tolan, implying that benzil obtained in the iodoacetoxylation of tolan is formed by way of IAS. The reaction at room temperature in dispersed light afforded *trans*-α,α′-diiodostilbene (DIS), which also gave IAS and benzil by the oxidation with peracetic acid. These results and some kinetic data suggest a mechanism involving slow formation of acetyl hypoiodite followed by its rapid addition to the triple bond.

In our previous papers[2,3] it has been reported that aliphatic olefins such as cyclohexene or propylene react easily with a mixture of iodine and peracetic acid in acetic acid–ether at room temperature to give iodoacetoxy compounds, *e.g.*, 1-iodo-2-acetoxypropane (*ca.* 80%) from propylene. The kinetic study suggests a mechanism involving a rate-determining attack of peracetic acid on the olefin–iodine π complex.

$$2CH_3CH{=}CH_2 + I_2 + CH_3CO_3H + CH_3CO_2H \longrightarrow 2CH_3\underset{\displaystyle CH_3COO}{\underset{|}{CH}}{-}\underset{\displaystyle I}{\underset{|}{CH_2}} + H_2O$$

It is interesting to know how this mixture of iodine and peracetic acid reacts with acetylenic compounds. The reaction of acetylene with a mixture of iodine and peracetic acid was found to give diiododiacetoxyethane together with some other products, but no ole-

(1) Contribution No. 164.

(2) Y. Ogata, K. Aoki, and Y. Furuya, *Chem. Ind. (London)*, 304 (1965).

(3) Y. Ogata and K. Aoki, *J. Org. Chem.*, **31**, 1625 (1966).

TABLE I

REACTION OF TOLAN WITH A MIXTURE OF IODINE AND PERACETIC ACID IN ACETIC ACID TO FORM α-IODO-α′-ACETOXYSTILBENE (IAS) AND BENZIL[a]

Initial concn of reactants, M			Catalyst, N		Yield, %[b]	
[PhC≡CPh]	[I_2]	[AcO_2H]	(H_2SO_4)	Temp, °C	IAS	Benzil
0.10	0.055	0.055	0	50	63	17
0.10	0.055	0.055	0	50	74	14[c]
0.060	0.033	0.033	0	50	56	16[d]
0.10	0.055	0.055	0	70	57	15
0.067	0.067	0.067	0	50	57	43
0.10	0.055	0.055	0.05	50	38	36
0.10	0.055	0.055	0.20	50	23	39
0.10	0	0.11	0	50	0	6

[a] Reaction time, 10 hr at 50° and 5 hr at 70°. [b] Yield based on original tolan was estimated by means of uv spectrophotometry. [c] Acetic acid solutions of tolan and peracetic acid were simultaneously added dropwise to an acetic acid solution of iodine with stirring. In the other runs the reactants were all mixed in acetic acid at the beginning of the reaction. [d] Reaction in 90% aqueous acetic acid.

finic compounds were obtained.[4] On the other hand, the addition of chlorine, hydrochloric acid, bromine, or *N*-bromosuccinimide (NBS) to phenyl- or diphenylacetylenes in acetic acid gave the corresponding cis and trans olefins in fairly good yields.[5-11] For example, the reaction of diphenylacetylenes with NBS in aqueous acetic acid gave α-bromo-α′-acetoxystilbene together with α,α-dibromodeoxybenzoin, and the mechanism involving a rate-determining electrophilic attack of hypobromous acid on the triple bond was postulated.[8,12] The present paper describes our results on the reaction of tolan with iodine–peracetic acid in acetic acid, which was found to give iodoacetoxystilbene and benzil. The mechanism of the reaction will be discussed on the basis of the results.

Results and Discussion

The reaction of tolan with a mixture of iodine and peracetic acid in acetic acid at 50° in the dark gave *trans*-α-iodo-α′-acetoxystilbene (abbreviated to IAS) in *ca.* 70% yield (eq 1). This product was identified

$$2C_6H_5C{\equiv}CC_6H_5 + I_2 + CH_3CO_3H + CH_3CO_2H \longrightarrow 2\ \underset{\text{IAS}}{\text{I(C}_6\text{H}_5\text{)C=C(OCOCH}_3\text{)C}_6\text{H}_5} + H_2O \quad (1)$$

by infrared and nmr spectra and elementary analysis. The configuration was assigned on the basis of nmr spectra, *i.e.*, τ 8.24 (singlet) for the methyl group of *trans*-IAS, because the signal is quite similar to that at τ 8.17 (singlet) of *trans*-α-bromo-α′-acetoxystilbene, rather than 7.79 of its cis isomer, both of which were obtained by the reaction of tolan with NBS in aqueous acetic acid.[3] The deshielding of iodine in *cis*-iodoacetoxystilbene as observed in *cis*-bromoacetoxystilbene would also operate to the similar extent. Therefore, the obtained iodoacetoxystilbene having the mp 146° is surely the trans isomer. Further, no cis isomer was formed in the iodoacetoxylation of tolan, since the methyl nmr spectra of the reaction mixture gave only a signal at τ 8.24.

When equimolar amounts of reactants were used, a considerable yield of benzil (*ca.* 40%) was obtained together with IAS, as shown in Table I. Although oxidation of tolan with peracids also gives benzil,[13,14] the yield was low compared with that in the iodoacetoxylation of tolan (eq 2, Table I). This fact

$$C_6H_5C{\equiv}CC_6H_5 + 2RCO_3H \longrightarrow C_6H_5COCOC_6H_5 + 2RCO_2H \quad (2)$$

suggests that benzil produced in iodoacetoxylation is formed not from a direct oxidation of tolan with peracetic acid but from a successive oxidation of some intermediate with peracetic acid. In fact, the peracetic acid oxidation of IAS gave benzil in a good yield, liberating a molecular iodine, as shown in Table II and eq 3. Hence, most of the benzil produced is

$$\underset{\text{IAS}}{\text{I(C}_6\text{H}_5\text{)C=C(OCOCH}_3\text{)C}_6\text{H}_5} + CH_3CO_3H \xrightarrow{-I_2} C_6H_5COCOC_6H_5 \quad (3)$$

TABLE II

REACTION OF α-IODO-α′-ACETOXYSTILBENE (IAS) WITH PERACETIC ACID IN ACETIC ACID TO FORM BENZIL

Initial amount of reactants		Volume of	Reaction		
IAS, mmol	AcO_2H, mmol	solvent, AcOH, ml	Temp, °C	Time, hr	Yield,[a] %
1.0	1.1	20	50	10	49
2.0	2.2	25	70	5	64[b]

[a] Yield was estimated by means of uv spectrophotometry. [b] Peracetic acid in acetic acid was slowly added with stirring to IAS in acetic acid.

probably the result of the successive oxidation of IAS with peracetic acid; the amount of benzil produced from the direct oxidation of tolan with peracetic acid may be neglected. This is confirmed also by the kinetic data (Table III).

As shown in Table I, the yield of IAS and/or benzil is not so affected by the addition of water to the reaction system. This behavior is different from the result in iodoacetoxylation of olefins, where the addition of water considerably lowers the yield.[3] The reaction at higher temperature gave rather low yield

(4) Y. Ogata, K. Aoki, and Y. Shibata, The 19th Annual Meeting of Chemical Society of Japan at Yokohama, 1966.
(5) H. Sinn, S. Hopperdietzel, and D. Sauermann, *Monatsh. Chem.*, **96**, 1036 (1965).
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(7) R. C. Fahey and D. J. Lee, *J. Amer. Chem. Soc.*, **88**, 5555 (1966).
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(10) J. A. Pincock and K. Yates, *ibid.*, **90**, 5643 (1968).
(11) J. König and V. Wolf, *Tetrahedron Lett.*, 1629 (1970).
(12) A. Jovtscheff and S. L. Spassov, *Monatsh. Chem.*, **100**, 328 (1969).
(13) R. N. McDonald and P. A. Schwab, *J. Amer. Chem. Soc.*, **86**, 4866 (1964).
(14) J. K. Stille and D. D. Whitehurst, *ibid.*, **86**, 4871 (1964).

of IAS and/or benzil, probably because the decomposition of peracetic acid became faster. With increasing molar ratio of the reagent, the yield of benzil rises, but the yield of IAS falls down, probably because IAS is further oxidized with excess peracetic acid. Moreover, the addition of sulfuric acid lowers the yield of IAS and raises the yield of benzil. This indicates that the oxidation of IAS with peracetic acid is catalyzed by sulfuric acid, while iodoacetoxylation is not an acid catalysis.

It is known that benzil is oxidized with peracetic acid to give benzoic acid.[15] However, the oxidation is slow, the value of the second-order rate constant being *ca.* 10^{-4} M^{-1} sec^{-1} at 70°, which is about a hundred times as small as that for the oxidation of IAS with peracetic acid to form benzil. Hence, the formation of benzoic acid in the iodoacetoxylation of tolan with iodine–peracetic acid can be neglected. Virtually no benzoic acid was detected in the present reaction.

As obvious in Table III, the rate of the reaction of IAS with peracetic acid is about a hundred times

TABLE III

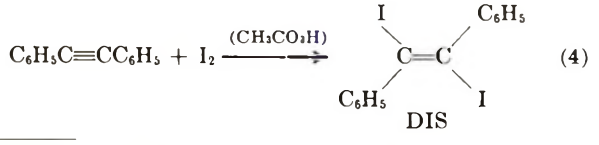
SECOND-ORDER INITIAL RATE CONSTANTS FOR THE REACTION OF PERACETIC ACID IN ACETIC ACID AT 50°

Substrate[a]	Initial concn, M [I_2]	Initial concn, M [AcO_2H]	k_2[b] × 10^3, M^{-1} sec^{-1}
Tolan	0	0.05	0.03
IAS	0	0.05	2.8
Tolan	0.05	0.05	1.3 (0.6,[c] 1.2[d])
	0.05	0.05	1.2 (1.3[c])

[a] Initial concentration of the substrate was 0.05 M. [b] Rate constant for the consumption of peracetic acid. [c] Rate constant for the consumption of iodine. [d] Rate constant for the consumption of tolan measured by means of uv spectrophotometry.

as fast as that of the peracetic acid oxidation of tolan. The rate of the consumption of peracetic acid and/or iodine in the reaction of tolan with a mixture of iodine and peracetic acid is almost the same as that in the reaction of iodine and peracetic acid alone (Table III). Such a phenomenon has been observed in the iodination of aromatic compound with a mixture of iodine and peracetic acid.[16] In contrast, iodoacetoxylation of olefin is fast, the second-order rate constant k_2 being *ca.* 5×10^{-2} M^{-1} sec^{-1} at 30° which is *ca.* 300-fold of that in the reaction of iodine with peracetic acid.[3] Hence, the mechanism proposed for the iodination of aromatic compound with iodine-peracetic acid, where the reaction of iodine with peracetic acid forming acyl hypohalite is rate determining, may be applied for the iodoacetoxylation of tolan.

It was found that *trans*-α,α'-diiodostilbene (DIS) was produced in 2 weeks in *ca.* 80% yield based on original iodine, when the reaction of tolan with iodine–peracetic acid was carried out at room temperature in 50 vol % acetic acid–ether under dispersed light (eq 4). Under these conditions the rate of consumption



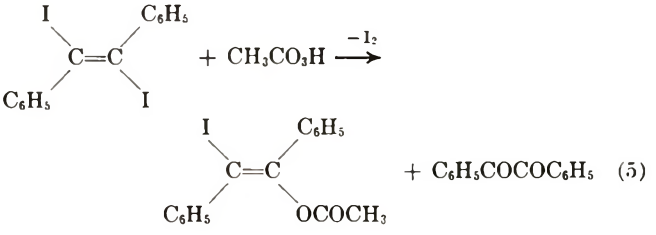
(4)

of iodine was slow, but after 1 day colorless crystals of DIS began to precipitate. The precipitate was identified by ir spectrum, mixture melting point determination, and elementary analysis.

Here, the formation of DIS in the reaction of tolan with iodine alone (6% yield in 6 days) was slower than that in the presence of peracetic acid (80% yield in 2 weeks). Further, the formation of DIS in the reaction of tolan with a mixture of iodine and peracetic acid also was slower in the dark (11% yield in 18 days). These results suggest that the formation of DIS proceeds mainly in a radical mechanism. Peracetic acid and/or a small amount of acetyl peroxide present in peracetic acid may affect the radical reaction.

Since the activation energy of a radical addition reaction is generally small (2–3 kcal/mol),[17] it is expected that the ionic reaction (iodoacetoxylation) is preferred to the radical addition at higher temperature. In fact, DIS was not virtually formed in the dark at 50°, which supports ionic character of the iodoacetoxylation and radical nature of the formation of DIS. An evidence for the radical nature is the acceleration of the reaction of tolan with iodine to form DIS by irradiation of light (39% yield in 3.5 hr) and/or by addition of benzoyl peroxide (18% yield in 5 hr at 70°).

DIS also reacted with peracetic acid yielding IAS (37%), benzil (30%), and liberating iodine (eq 5, Table IV). However, IAS is not formed *via* DIS in the iodo-



(5)

TABLE IV

REACTION OF α,α'-DIIODOSTILBENE (DIS) WITH PERACETIC ACID IN ACETIC ACID TO FORM α-IODO-α'-ACETOXYSTILBENE (IAS) AND BENZIL[a]

Initial amount of reactants DIS, mmol	Initial amount of reactants AcO_2H, mmol	Volume of solvent, AcOH, ml	Reaction Temp, °C	Reaction Time, hr	Yield[b] IAS, %	Yield[b] Benzil, %
2.0	2.0	20	50	10	20	22
2.0	2.2	25	70	5	37	30[c]

[a] Suspended solution of DIS was always stirred. [b] Yield based on original DIS was estimated by means of uv spectrophotometry. [c] Peracetic acid in acetic acid was slowly added with stirring to the suspension of DIS in acetic acid.

acetoxylation of tolan, since no DIS was obtained in the reaction of tolan with iodine alone in acetic acid at 50° in the dark.

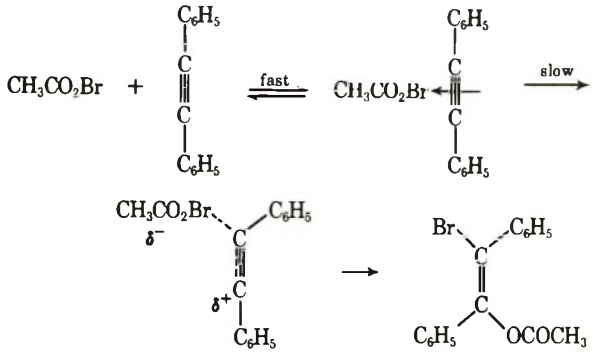
The cis addition of chlorine or hydrochloric acid to tolan or phenylpropyne is more favorable than trans addition,[6,7,9] but the trans adduct is favored in the reaction of tolan or phenylpropyne with bromine or NBS in aqueous acetic acid.[8,10] The present iodoacetoxylation is specific trans addition, which suggests that the configuration of the transition state in these additions depends on the size of halogen atoms; thus, a

(15) Y. Furuya and I. Urasaki, *Bull. Chem. Soc. Jap.*, **41**, 660 (1968).
(16) Y. Ogata and K. Nakajima, *Tetrahedron*, **20**, 43 (1964).
(17) M. Takahashi, "Chemistry of Free Radicals," H. Sakurai and K. Tokumaru, Ed., Nankodo, Tokyo, Japan, 1967, p 30.

larger halogen gives a lower cis:trans ratio of the adducts.

As described above, the reaction of acetylene itself with a mixture of iodine and peracetic acid gave no olefin, but saturated compounds.[4] This is explained by a higher reactivity of olefins than the corresponding acetylenes in the electrophilic addition reaction, whereas tolan gave olefinic products (IAS). This fact may be due to the resonance stabilization of the product, where the double bond is conjugated with the benzene rings. Hence, most of the other additions to phenyl- or diphenylacetylenes give also olefinic products.[5-11,18] Furthermore, the steric interaction between large iodine atoms and/or between an iodine atom and a benzene ring may inhibit the addition to iodo olefins. In spite of the easy addition of bromine to stilbene,[19] the addition of iodine or acyl hypoiodite to stilbene was found to be difficult.

Two kinds of mechanisms have been postulated for the addition reaction of acetylenes: one is a mechanism involving a nucleophilic addition of bromide ion to the triple bond as proposed for bromine addition to acetylenes,[5,20] and the other is an electrophilic addition proposed for the bromoacetoxylation of diphenylacetylenes with NBS in 80–90% aqueous acetic acid.[12] In the latter, acetyl hypobromite (CH_3CO_2Br), formed by the reaction of NBS with water and then with acetic acid, may attack the triple bond forming an ion pair *via* a π complex, because acetyl hypobromite is more electrophilic than hypobromous acid (eq 6).

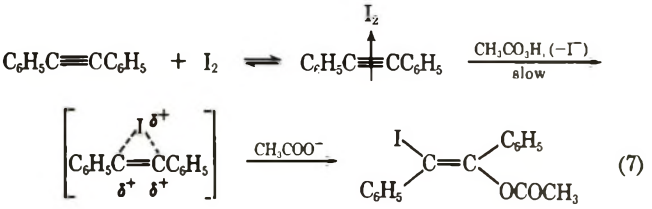


(6)

The present iodoacetoxylation is quite similar to bromoacetoxylation except for a higher trans:cis ratio of the products. The iodoacetoxylation of tolan is an electrophilic addition, since its rate is low compared with that of iodoacetoxylation of olefins.

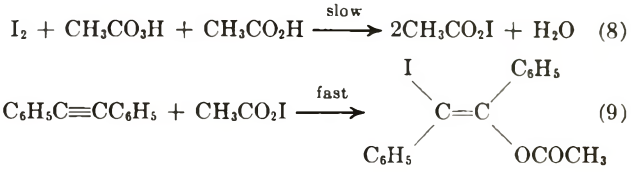
In view of these facts, the following two mechanisms are conceivable (eq 7–9): (a) a rate-determining attack of peracetic acid on the tolan–iodine π complex which has been proposed by us for the iodoacetoxylation of olefins,[3] and (b) the slow formation of acetyl hypoiodite followed by its rapid addition to tolan, as postulated for aromatic iodination.[16] Step 9 cannot be slower than step 8, because the rate of the consumption of tolan in the present reaction is the same as that of the formation of acetyl hypoiodite (Table III). Though these two cannot be distinguished by the present data, mechanism b seems to be more probable than mechanism a, because the rate of consumption of peracetic acid or iodine in the reaction of iodine

Mechanism a



(7)

Mechanism b



(8)

(9)

with peracetic acid alone (*i.e.*, the formation of acetyl hypoiodite or hypoiodous acid) is not affected by addition of tolan to this reaction system, and in this sense iodoacetoxylation of tolan is similar to the bromoacetoxylation reaction with NBS.

The formation of acetyl hypoiodite in the reaction of iodine with peracetic acid has not been proved directly. In the thermal decomposition of phenyl iodine diacetate, acetyl hypoiodite has been postulated as an intermediate which decomposes to give methyl iodide and carbon dioxide, though acetyl hypoiodite has never been isolated.[21] Hence, if acetyl hypoiodite is formed in a mixture of acetic acid, peracetic acid, and iodine, then the formation of methyl iodide and carbon dioxide *via* decarboxylation of acetyl hypoiodite may be observed under appropriate reaction conditions when the unsaturated substrate is absent (eq 10). The

$$CH_3CO_2I \longrightarrow CH_3I + CO_2 \qquad (10)$$

isolation of methyl iodide in this reaction was expected to be difficult, because it is easily oxidized with peracetic acid to methyl acetate (eq 11).[22] Nevertheless,

$$CH_3I + CH_3CO_3H \longrightarrow CH_3CO_2CH_3 + HOI \qquad (11)$$

both methyl iodide and methyl acetate could eventually be detected by means of glpc from the mixture of acetic acid, peracetic acid, and iodine, as described in the Experimental Section. Carbon dioxide was also produced in 12.3% yield at 70°. Only 0.6% yield of carbon dioxide was produced from peracetic acid in acetic acid alone under the same conditions. These results may be a satisfactory evidence for the formation of acetyl hypoiodite.

Experimental Section

Materials.—About 3.5 *M* peracetic acid was prepared by the reaction of acetic anhydride with 60% H_2O_2 in the presence of a catalytic amount of H_2SO_4.[23] Stilbene was prepared by the reduction of benzoin with zinc amalgam,[24] mp 124–125° (from 95% ethanol) (lit. mp 124°). Tolan was prepared from stilbene by the debromination of stilbene dibromide with KOH in EtOH,[25] mp 60.5–61° (from 95% ethanol)(lit. mp 60–61°). Commercial 99.5% acetic acid was purified by rectification (bp 117–119°). Iodine was purified by the sublimation.

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(19) G. Heublein and E. Mlejnek, *Z. Chem.*, **7**, 340 (1967).
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(22) Y. Ogata and K. Aoki, *J. Org. Chem.*, **34**, 3974 (1969).
(23) Y. Ogata and I. Urasaki, *J. Chem. Soc. C*, 1689 (1970).
(24) R. L. Shriner and A. Berger, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 786.
(25) L. I. Smith and M. M. Falkof, ref 24, p 350.

Iodoacetoxylation of Tolan. *trans*-α-Iodo-α′-acetoxystilbene (IAS).—Tolan, iodine, and peracetic acid (each 5 mmol) were dissolved in acetic acid (50 ml) in the dark and then kept standing at 50° for 10 hr. At the end of the reaction *ca.* 33% of iodine was consumed. The reaction mixture was diluted with water, being extracted with ether or chloroform. The extract was washed successively with aqueous KI, aqueous $Na_2S_2O_3$, aqueous $NaHCO_3$, and then with water. The dried (Na_2SO_4) organic layer was removed from the solvent under reduced pressure, yielding residual pale yellow solid (1.31 g) which gave yellow crystals of IAS (0.68 g) by the fractional crystallization from methanol. Additional IAS (0.136 g) was isolated from the filtrate by means of column chromatography on silica gel using benzene as eluent, so that the total yield of isolated IAS was 0.817 g (44.9% based on original tolan), mp 146–146.5° (from methanol).

A methanol solution of this material showed only an inflection at about 250 mμ (ε 11,000), being similar to the spectra of α-substituted or α,α′-disubstituted stilbenes.[26] The ir spectrum (KBr) showed absorption bands at 1194, 1220, and 1760 (CO-OC=C), 1370 (CH_3), and 1500 and 3000–3070 cm^{-1} (C_6H_5). Nmr spectrum (20% in $CDCl_3$, standard TMS) showed signals at τ 2.3–3.0 (multiplet, C_6H_5) and 8.24 (singlet, CH_3COO—), and their intensity ratio was 10:3. These data indicate the presence of an acetoxyl group at the α position of stilbene.

Anal. Calcd for $C_{16}H_{13}IO_2$: C, 52.77; H, 3.60; I, 34.85. Found: C, 52.79; H, 3.33; I, 34.8.

Identification of Benzil.—The residue (0.575 g) recovered from the above filtrate of IAS was chromatographed on silica gel in benzene, yielding 0.136 g of IAS (R_f 0.74 in tlc) and 0.321 g (30.6% yield) of benzil (R_f 0.69), which on recrystallization from methanol gave mp and mmp 95°.

Addition of Iodine to Tolan. *trans*-α,α′-Diiodostilbene (DIS).—Tolan (10 mmol), iodine (5 mmol), and peracetic acid (5 mmol) were dissolved in 50 vol % acetic acid–ether (50 ml) and kept at room temperature in the dispersed light. In a few days precipitate began to occur. After 2 weeks the precipitate was filtered off, washed with methanol, and dried, yielding 1.80 g of DIS (84% yield based on iodine); recrystallization from $CHCl_3$ gave mp and mmp (in a sealed tube) 191° dec (lit.[26] mp 199° dec).

A methanol solution of this material showed almost the same uv spectrum as tolan, indicating the decomposition of DIS to tolan and iodine in methanol. It has been reported that DIS is slightly decomposed also in *n*-hexane.[26] The ir spectrum (KBr) showed absorption bands at 550 (CI) and 1700–2000 and 3000–3080 cm^{-1} (C_6H_5). The nmr spectrum could not be obtained because of the poor solubility of DIS.

Anal. Calcd for $C_{14}H_{10}I_2$: C, 38.92; H, 2.33; I, 58.75. Found: C, 38.68; H, 2.39; I, 59.0.

An authentic sample of DIS was obtained by the reaction of tolan with iodine in acetic acid at room temperature. After 6 days the yield of precipitated DIS was only 6% of the theoretical amount. Recrystallization from $CHCl_3$ gave mp of 191° dec in a sealed tube.

Reaction of Tolan with Peracetic Acid.—An acetic acid solution (20 ml) of tolan (2 mmol) and peracetic acid (2.2 mmol) was kept standing at 50° for 10 hr. The reaction mixture was diluted with water and extracted with chloroform. The extract was washed with aqueous $NaHCO_3$ and water and then dried (Na_2SO_4). Evaporation of solvent *in vacuo* gave a solid which consisted of unreacted tolan (94%) and benzil (6%), according to the tlc-analysis and uv spectrophotometry.

Reaction of IAS with Peracetic Acid.—Peracetic acid (2.2 mmol) was added slowly to IAS (2 mmol) in acetic acid at 70° over a period of 5 hr. The reaction mixture which contained iodine liberated was diluted with water and extracted with chloroform. The extract, worked up as above, gave yellow solid containing IAS and benzil by means of tlc analysis, the yield of benzil being 64% according to the uv spectrophotometry.

Reaction of DIS with Peracetic Acid.—The suspension of DIS (2 mmol) in acetic acid (20 ml) was added with peracetic acid (2.2 mmol) in acetic acid (5 ml) at 70° over a period of 5 hr, iodine being liberated as the reaction proceeded. After unreacted DIS being recovered by filtration (0.284 g, 32.9%), the filtrate was diluted with water and extracted with chloroform. The extract was worked up as above to yield yellow solid containing IAS (37%) and benzil (30%) (tlc and uv spectrophotometry).

Ultraviolet Spectrophotometry.—A methanolic solutions of three components (tolan, IAS, and benzil) of known concentrations were prepared and extinctions at 230, 258 and 296 mμ were measured by a Hitachi double beam uv–visible spectrophotometer, Model 124. The compositions calculated from the extinctions and molecular absorption coefficient of each component agreed with the theoretical within 1% error. Since the main products were IAS and benzil, the estimation was done assuming the reaction mixture consisted of only the three components.

Typical Procedure for the Rate Measurements.—Separate acetic acid solutions of 0.105 *M* tolan, 0.1 *M* iodine, and 2.0 *M* peracetic acid were allowed to stand at 50° to reach temperature equilibrium. Aliquots (9.5 ml, 10 ml, and 0.5 ml, respectively) were pipetted out from the solutions and they were mixed quickly to start the reaction, giving each 0.1 *M* reactant solution. Aliquots (each 2 ml) were pipetted out at known intervals of time and placed in a separatory funnel containing distilled water (40 ml) and CCl_4 (20 ml). The content of iodine in CCl_4 and that of peracetic acid in aqueous layer were measured iodometrically. Sometimes, the titrated CCl_4 layer was then analyzed by means of uv spectrophotometry.

Detection of Carbon Dioxide, Methyl Iodide, and Methyl Acetate in the Reaction of Iodine with Peracetic Acid.—An acetic acid solution (33 ml) of *ca.* 3 *M* peracetic acid (0.1 mol) was added dropwise with stirring to an acetic acid solution (50 ml) of iodine (0.01 mol) in a three-necked flask fitted with a reflux condenser at *ca.* 70° during 30 min. Then, nitrogen gas was slowly bubbled into the reaction mixture for *ca.* 30 min. The gaseous and volatilized products passing through the reflux condenser were trapped with Dry Ice–methanol, and carbon dioxide was then taken up with a saturated aqueous $Ba(OH)_2$, the precipitated $BaCO_3$ being filtered off and dried. Trapped products were identified by means of glpc employing a Yanagimoto Model GCG 550 F with a flame ionization detector operated with a 1.5 m × 3 mm column packed with Apiezon L grease 15% on Celite 545 of 80–100 mesh using N_2 as a carrier (20 ml/min) at 40° and H_2 in a flow rate of 20 ml/min. Retention times were 2.1 and 3.2 min for methyl acetate and methyl iodide, respectively.

Registry No.—IAS, 29478-23-7; DIS, 20432-11-5; tolan, 501-65-5; iodine, 7553-56-2; peracetic acid, 79-21-0.

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Intramolecular Diels–Alder Reactions. VI.[1a] Syntheses of 3-Hydroxymethyl-2-naphthoic Acid Lactones

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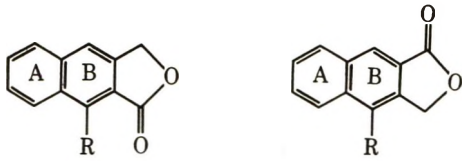
Twelve monoaryl enynic and diynic esters were synthesized and subjected to refluxing acetic anhydride. Seven underwent intramolecular Diels–Alder reactions. Propargyl phenylpropiolate (**9**) and phenylpropargyl propiolate cyclized to 3-hydroxymethyl-2-naphthoic acid lactone (**1b**), while *trans*-cinnamyl propiolate gave 3-hydroxymethyl-3,4-dihydro-2-naphthoic acid lactone. Derivatives of **1b** resulted from methoxy- and methylenedioxy-substituted compounds. Propargyl *trans*-cinnamate, allyl phenylpropiolate, and three derivatives of **9** did not cyclize. Purified samples of **9** and its derivatives exist as stable hydrates.

Previous studies in our laboratory[2-5] concerned the intramolecular Diels–Alder reaction of unsaturated diaryl esters of the type $Ar(C_2)CO_2CH_2(C_2)Ar'$, where each (C_2) unit is a $-CH{=}CH-$ or $-C{\equiv}C-$ group. For Ar and Ar′ = phenyl or substituted phenyl groups, the products formed have the skeletal structures of 1- or 4-phenyl-3-hydroxymethyl-2-naphthoic acid lactones (*i.e.*, of cyclolignan lactones) **1a** and **2a**, respectively (where ring B may be in the dihydro or tetrahydro form). In the present work we investigated the syntheses and cyclizations of unsaturated monoaryl esters



1 **2**

a, R = Ph; **b**, R = H

of the types $H(C_2)CO_2CH_2(C_2)Ar'$ and $Ar(C_2)CO_2CH_2(C_2)H$. For Ar = Ar′ = Ph intramolecular Diels–Alder reactions should lead to 3-hydroxymethyl-2-naphthoic acid lactone (**1b** = **2b**) and its hydro products.

The esters prepared for cyclization and the cyclized products formed in our study are shown in Table I. Syntheses of the esters were effected by four different standard methods, as described in the Experimental Section. Ethyl 3,5-dimethoxyphenylpropiolate (**18**), needed to obtain **5** and **11**, was prepared from 3,5-dimethoxybenzaldehyde and triethyl iodophosphonoacetate. Compound **18** could not be obtained through initial treatment of ethyl *trans*-3,5-dimethoxycinnamate with bromine, a process which gave the 2-bromo derivative instead of the expected dibromopropionate (as occurs with ethyl *trans*-cinnamate,[6] as well as its 3,4-methylenedioxy and 3,4,5-trimethoxy derivatives).[7] In contrast to the other esters in Table I the four propargyl phenylpropiolates **9–12** retained water of hydration tenaciously. It appears that at least 0.25 mol of water is strongly bound to some common structural feature in these molecules.

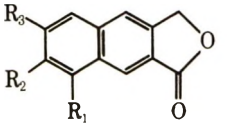
Table I

Products from Cyclization of Monoaryl Unsaturated Esters[a]

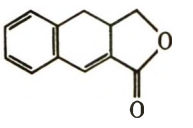
No.	Compd used Formula[b]	Cyclization product	Yield,[c] %
	$H(C_2)CO_2CH_2(C_2)Ar'$ Series		
3	$HC{\equiv}CCO_2CH_2C{\equiv}CC_6H_5$	1b	2
4	3,4-Methylenedioxy-**3**	15	3*
5	3,5-Dimethoxy-**3**	16	10
6	*trans*-$HC{\equiv}CCO_2CH_2CH{=}CHC_6H_5$	17[d]	8
7	3,4-Methylenedioxy-**6**	15	13
8	3,5-Dimethoxy-**6**	16	5*
	$Ar(C_2)CO_2CH_2(C_2)H$ Series		
9	$C_6H_5C{\equiv}CCO_2CH_2C{\equiv}CH$	1b	14
10	3,4-Methylenedioxy-**9**	None	
11	3,5-Dimethoxy-**9**	None	
12	3,4,5-Trimethoxy-**9**	None	
13	*trans*-$C_6H_5CH{=}CHCO_2CH_2C{\equiv}CH$	None	
14	$C_6H_5C{\equiv}CCO_2CH_2CH{=}CH_2$	None	

[a] Cyclization conditions: refluxing acetic anhydride for 12–72 hr. [b] Compounds **4**, **5**, **7**, **8**, and **10–12** have substituents on the phenyl ring. [c] An asterisk denotes overall yields from the alcohol corresponding to the ester used. [d] From cyclization in a nitrogen atmosphere.

As in earlier studies[2-5] cyclization was effected by refluxing in acetic anhydride. Air oxidation probably accounts for formation of the aromatic compounds **15**



15, $R_1 = H$; $R_2R_3 = OCH_2O$
16, $R_1 = R_3 = CH_3O$; $R_2 = H$



17

and **16** from the enynic esters **7** and **8**, respectively. Some **1b** was, likewise, isolated from cyclization of **6** in the presence of air. However, **6** gave the dihydronaphthalene lactone **17** when the reaction was conducted in an atmosphere of nitrogen. Even long refluxing did not give cyclization of **10–14**, while yields were low for **3–9**. In all of these intramolecular Diels–Alder reactions the aryl group must function as part of the "dienic moiety." Hence, one would expect esters **3–8** of the $H(C_2)CO_2CH_2(C_2)Ar'$ type to cyclize more readily than **9–14**, where the aryl group is part of the acidic moiety. Tendencies for the monoaryl compounds to

(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) NSF Undergraduate Research Participant, summer 1968. (c) Research Associate, 1966–1967. (d) Research Associate, 1969–1970.

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cyclize are analogous to those in the diaryl series,[2-5] although overall yields from starting acidic and alcoholic components were generally higher in the diaryl cases.

Experimental Section[8]

Starting Materials.—Sodium propiolate was prepared by mixing equimolar amounts of anhydrous $NaHCO_3$ and propiolic acid in warm MeOH until CO_2 evolution ceased. The precipitated salt was collected by filtration and dried *in vacuo* for 2 days. Propiolyl chloride was prepared *in situ* by stirring (for 5 hr) an equimolar mixture of sodium propiolate and $SOCl_2$ in dry benzene. Formed *in situ* analogously from 3,4,5-trimethoxyphenylpropiolic acid[7] were the sodium salt and then (by stirring with excess $SOCl_2$ for 40 min, followed by repetitive addition and evaporation of benzene) the acid chloride. As needed, NaOEt was obtained by reacting a weighed amount of Na with excess absolute EtOH and removal of unreacted solvent *in vacuo*. Sodium salts of unsaturated alcohols were formed, in turn, by repetitive steps of addition of benzene to an equimolar mixture of the alcohol and NaOEt and then evaporation of the mixture to dryness.

Phenylpropargyl Chloride.[9]—To a cold (0°), stirred solution of 14.1 g (0.18 mol) of pyridine in 25 ml of $CHCl_3$ was added dropwise 20.2 g (0.17 mol) of $SOCl_2$. This solution was added dropwise, in turn, to a cold solution of 19.8 g (0.15 mol) of phenylpropargyl alcohol (Farchan) in 25 ml of $CHCl_3$. The mixture was stirred 10 min longer, refluxed for 2 hr, washed with water, dried (Na_2SO_4), and distilled to give 18.2 g (81%) of liquid: bp 62–65° (0.1 mm) [lit.[10] 51%, bp 99° (7 mm)]; ir ($CHCl_3$) 2230 (C≡C), 1250 cm^{-1} (C≡CCH$_2$Cl);[11] nmr (CCl_4) δ 4.26 (s, 2, CH_2Cl), 7.1–7.7 (m, 5, phenyl).

Ethyl *trans*-3,5-Dimethoxycinnamate.—Refluxing a solution of *trans*-3,5-dimethoxycinnamic acid (Aldrich) in 3% anhydrous ethanolic HCl[7] gave crystals (95%, mp 40–45°) converted to needles (mp 45–46°) on recrystallization from absolute EtOH: ir ($CHCl_3$) 1700 (ester C=O), 980 cm^{-1} (*trans*-CH=CH); nmr (CCl_4) δ 1.28 (t, 3, J = 7 Hz, CH_2CH_3), 3.72 (s, 6, 2 OCH_3), 4.20 (q, 2, CH_2CH_3), 6.34 (d, 1, J = 16 Hz, CH=CHC=O) which partially overlaps 6.3–6.7 (m, 4 total, including 3 aromatic H), *ca.* 7.55 (split d, CH=CHC=O).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.99; H, 6.62.

Methyl *trans*-3,5-Dimethoxycinnamate.—To a refluxing solution of 30.5 g of *trans*-3,5-dimethoxycinnamic acid in 340 ml of MeOH were added (in three portions over a period of 3.5 hr) total amounts of 20.2 g of KOH and 40 ml of Me_2SO_4. The mixture was evaporated nearly to dryness, treated with water, and extracted with ether. The ether layer was washed with aqueous $NaHCO_3$ solution and then with water and evaporated to yield 32.1 g (99%) of ester, mp 72–74.5°, obtained as prisms (mp 74.5–75.5°) on recrystallization from ether: nmr ($CDCl_3$) δ 3.78 (s, 9, 3 MeO), 6.38 (d, 1, J = 16 Hz, CH=CHC=O) which partially overlaps 6.48 (t, 1, J_m = 2.2 Hz, H-4), 6.64 (d, 2, H-2 and H-5), 7.59 (d, 1, CH=CHC=O).

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.00; H, 6.51.

***trans*-3,5-Dimethoxycinnamyl Alcohol.**—To a stirred, cold (−78°) mixture of 1.37 g (0.036 mol) of $LiAlH_4$ and 100 ml of ether was added slowly a solution of 3.88 g (0.016 mol) of ethyl *trans*-3,5-dimethoxycinnamate in 50 ml of ether. The mixture was stirred at −78° for 2.5 hr longer, allowed to warm to room temperature, and, while still very cold, treated cautiously with water until a white solid formed. Evaporation of the dried ether layer plus ether extracts of the solid gave 2.9 g (85% pure by nmr spectrum, 78% yield) of nearly colorless liquid, which crystallized on standing. Recrystallization from CCl_4 gave needles: mp 54–55°; nmr ($CDCl_3$) δ 2.12 (broad s, 1, OH), 3.77 (s, 6, 2 OCH_3), 4.28 (d, 2, J = 4 Hz, CH_2), 6.2–6.6 (m, 5, aromatic and vinylic H).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.37; H, 7.48.

When the preceding reduction was run at 5°, both the vinylic and ester functions were affected to give **3-(3,5-dimethoxyphenyl)-1-propanol**: 73%, bp 146–154° (0.5 mm); analytically pure sample, bp 141° (0.4 mm) [lit.[12] bp 145–150° (3 mm)]; nmr (CCl_4) 1.5–1.9 (m, 2, $CH_2CH_2CH_2$), 2.3–2.7 (m, 2, CH_2OH), 3.2–3.6 (m, 3, $ArCH_2$ plus OH), 3.67 (s, 6, 2 MeO), 6.1–6.5 (m, 3, aromatic H).

Ethyl *trans*-2-Bromo-3,5-dimethoxycinnamate.—To a stirred solution of 2 g (8.5 mmol) of ethyl *trans*-3,5-dimethoxycinnamate in 10 ml of $CHCl_3$ was added (with cooling, over a period of 40 min) a solution of 1.4 g (8.8 mmol) of bromine in 5 ml of the same solvent. The orange color of the mixture persisted during an additional hour of stirring. Evaporation of the solvent and trituration of the residue with ligroin (60–90°) gave 2.1 g (79%) of crystals. Recrystallization from ligroin–benzene produced elongated prisms: mp 100–101.5°; positive Beilstein and permanganate tests, negative $AgNO_3$ test; ir ($CHCl_3$) 1710 (ester C=O), 980 cm^{-1} (*trans*-CH=CH); nmr (CCl_4) δ 1.32 (t, 3, J = 7 Hz, CH_2CH_3), 3.81 and 3.87 (2 s, 6, 2 MeO), 4.24 (q, 2, CH_2CH_3), 6.26 (d, 1, J = 16 Hz, CH=CHC=O) which partially overlaps 6.44 (d, J_m = 2.5 Hz, H-4), 6.68 (d, 1, H-6), 8.04 (d, 1, CH=CHC=O).

Anal. Calcd for $C_{13}H_{15}BrO_4$: C, 49.54; H, 4.80; Br, 25.36. Found: C, 49.32; H, 4.77; Br, 25.59.

***trans*-2-Bromo-3,5-dimethoxycinnamic Acid.**—Hydrolysis of preceding bromo ester was effected with aqueous methanolic KOH to give a white solid (39%), obtained as needles (mp 185–186°) on recrystallization from absolute EtOH: nmr ($CDCl_3$) δ 3.86 and 3.90 (2 s, 2 MeO), 6.42 (d, J = 16 Hz, CH=CH-C=O), 6.5–6.9 (poorly resolved, aromatic H), 8.30 (d, CH=CH-C=O); ir ($CHCl_3$) 1690 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_{11}BrO_4$: C, 46.01; H, 3.86; Br, 27.83. Found: C, 45.74; H, 3.80; Br, 27.61.

Ethyl 3,5-Dimethoxyphenylpropiolate (18).—To a cold (0°), stirred mixture of 0.3 mol of sodium triethyl iodophosphonoacetate (produced *in situ* by the stepwise procedure of Brown and Stevenson[13]) was added dropwise a solution of 50 g (0.3 mol) of 3,5-dimethoxybenzaldehyde (Aldrich) in 200 ml of glyme. The mixture was stirred for 10 hr while it warmed to room temperature. The solution was evaporated to a small volume, diluted with water, and extracted with ether. Evaporation of the ether extract produced a dark liquid layer (plus immiscible mineral oil) which distilled at 145–160° (0.5 mm) to give 40.8 g (58%) of colorless liquid which crystallized on standing at 6°. Recrystallizations from absolute EtOH and from CCl_4 gave prisms: mp 50–50.5°; ir (CCl_4) 2245 (C≡C), 1730 cm^{-1} (ester C=O); nmr (CCl_4) δ 1.32 (t, 3, J = 7 Hz, CH_2CH_3), 3.72 (s, 6, 2 OCH_3), 4.23 (q, 2, CH_2CH_3), 6.3–6.7 (m, 3, aromatic H).

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.80; H, 6.15.

3,5-Dimethoxyphenylpropargyl Alcohol.—To a cold (−78°), stirred mixture of 0.43 g (0.012 mol) of $LiAlH_4$ in 50 ml of dry ether was added, over a period of 20 min, 5 g (0.021 mol) of ester **18**. The mixture was stirred for 5 hr while it warmed to room temperature and was processed further as for the corresponding cinnamyl alcohol. Distillation at 170–180° (0.5 mm) gave 2 g (49%) of yellow liquid, which crystallized on standing at −5°. Recrystallization from CCl_4 gave white, sticky prisms: mp 38.5–40°; nmr (CCl_4) δ 2.77 (broadened s, 1, OH), 3.70 (s, 6, 2 OCH_3), 4.37 (s, 2, CH_2), 6.1–6.6 (m, 3, aromatic H).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 69.04; H, 6.55.

Propargyl *trans*-Cinnamate (13).—A mixture of cinnamoyl chloride (prepared from 3.7 g of *trans*-cinnamic acid), 1.4 g of propargyl alcohol, 40 ml of dry benzene, and 3 ml of pyridine was stirred for 10 hr, washed with water, dried (Na_2SO_4), and evaporated. Distillation of the residue gave 3.9 g (84%) of liquid: bp 117–119° (0.6 mm); ir (CCl_4) 3340 (≡CH), 1725 cm^{-1} (ester C=O); nmr (CCl_4) δ 2.52 (t, 1, J = 2.4 Hz, C≡CH),

(8) Microanalyses were performed by M-H-W Laboratories, Garden City, Mich., and Micro-Tech Laboratories, Skokie, Ill. Infrared spectra were determined by means of a Beckman IR-5A or IR-7 spectrometer; and mass spectra were determined by means of a CEC Model 21-110 instrument at 70 eV. Unless otherwise indicated, nmr spectra were obtained by means of a Varian A-60 spectrometer, with tetramethylsilane used as internal standard. In three designated cases a Varian HA-100 instrument was used.

(9) Method developed by T. M. McGuire of this laboratory.

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(13) D. Brown and R. Stevenson, *J. Org. Chem.*, **30**, 1759 (1965).

4.75 (d, 2, CH_2), 6.32 (d, 1, J = 16 Hz, CH=CHC=O), 7.1–7.5 (m, *ca.* 5, phenyl), 7.64 (d, 1, CH=CHC=O).

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.32; H, 5.30.

Allyl Phenylpropiolate (14).—A mixture of 7.1 g of ethyl phenylpropiolate (Aldrich), 0.1 g of NaOEt, and 50–70 ml of allyl alcohol was refluxed for 2 hr and then fractionally distilled at a slow rate until 20 ml of residue remained. The residue was treated with water, neutralized with dilute hydochloric acid, and extracted with ether. Distillation of the dried extract gave 7.2 g (95%) of liquid product: bp 96–99° (0.5 mm); nmr (CCl_4) δ 4.66 (d, 2, J = 5.5 Hz, $CHCH_2O$), 5.0–6.4 (m, 3, CH_2=CH), 7.1–7.7 (m, 5, phenyl).

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.03; H, 5.02.

Propargyl Phenylpropiolate (9). (a) By Ester Exchange.—In the preceding manner, except that propargyl alcohol was used in place of allyl alcohol, there was obtained 1.9 g (24%) of liquid: bp 60–63° (0.4 mm), redistilled at 68.5° (0.5 mm); ir (CCl_4) 3460 (weak, OH), 3320 (strong, ≡CH), 2130 (C≡C), 1730 cm^{-1} (ester C=O); nmr (CCl_4) δ 2.54 (t, 1, J = 2.5 Hz, C≡CH), 4.87 (d, 2, CH_2), 7.1–7.7 (m, 3, aromatic H), 7.8–8.2 (m, 2, aromatic H), water signal not apparent.

Anal. Calcd for $C_{12}H_8O_2 \cdot 0.5H_2O$: C, 74.60; H, 4.70. Found: C, 74.46; H, 4.78.

(b) *Via* Acid Chloride.—In the manner used for **13**, a mixture of phenylpropiolyl chloride,[4] propargyl alcohol, and pyridine was converted to **9**: bp 118–120° (0.8 mm); nmr ($CDCl_3$) δ 2.25 (t, 1, J = 2.5 Hz, C≡CH), 4.46 (d, 2, CH_2), 6.19 (s, *ca.* 0.4, $0.25H_2O$), 6.8–7.5 (m, 5, aromatic H).

Anal. Calcd for $C_{12}H_8O_2 \cdot 0.25H_2O$: C, 76.38; H, 4.54. Found: C, 76.44; H, 4.51.

Propargyl 3,4-Methylenedioxyphenylpropiolate (10).—This was prepared from methyl 3,4-methylenedioxyphenylpropiolate[7] and propargyl alcohol (as for **9**) to give a liquid product, bp 140–160° (0.5 mm), which solidified on standing: mp 45–55° (26%); ir (CS_2) 3320 (≡CH), 1730 (ester C=O), 1240 and 1040 (ArO), and 940 cm^{-1} (OCH_2O);[14] nmr (CCl_4) δ 2.40 (s, 0.6, *ca.* $0.25H_2O$), 2.62 (t, 1, J = 2.2 Hz, C≡CH), 4.84 (d, 2, CCH_2O), 5.98 (s, 2, OCH_2O), 6.72 (d, 1, J_o = 8 Hz, H-5), 7.33 (d, 1, J_m = 1.5 Hz, H-2), 7.56 (d of d, 1, H-6). Recrystallization from CCl_4 and then from absolute EtOH gave prisms: mp 61.5–62.5°; ir (CCl_4) 3670–3400 (OH), 3330 (≡CH), 1730 (ester C=O), 940 cm^{-1} (OCH_2O).

Anal. Calcd for $C_{12}H_8O_4 \cdot 0.5H_2O \cdot 0.25C_2H_5OH$: C, 65.19; H, 4.25. Found: C, 65.33; H, 4.05.

Propargyl 3,5-Dimethoxyphenylpropiolate (11).—This was obtained from ethyl ester **18** by exchange with propargyl alcohol and extraction of the product into benzene. Concentration of the solution gave crysals, mp 70–73° (25%), obtained as cream-colored needles (mp 73–74°) on recrystallizations from CCl_4 and absolute EtOH: ir (CCl_4) 3570–3400 (weak, broad, OH), 3320 (≡CH), 1720 cm^{-1} (ester C=O); nmr (CCl_4) δ 2.41 (t, 1, J = 2.5 Hz, C≡CH), 3.75 (broadened s, *ca.* 1.4, $0.75H_2O$), 3.81 (s, 6, 2 MeO), 4.84 (d, 2, CH_2), 6.55 (t, 1, J_m = 2 Hz, H-4), 7.12 (d, 2, H-2 and H-6).

Anal. Calcd for $C_{14}H_{12}O_4 \cdot 0.75H_2O$: C, 65.23; H, 5.28. Found: C, 65.05; H, 5.45.

Propargyl 3,4,5-Trimethoxyphenylpropiolate (12).—A mixture of 3,4,5-trimethoxyphenylpropiolyl chloride (prepared from 3.5 g of acid; *vide supra*), 0.87 g of propargyl alcohol, 1.3 mg of pyridine, and 20 ml of benzene was refluxed for 4.5 hr. The solution was washed with water and evaporated to give a product which crystallized from EtOH, yield 2.2 g (53%), mp 128–132.5°. Recrystallizations from CCl_4 and absolute EtOH gave faintly tan needles: mp 133.5–134°; ir (CCl_4) 3570–3400 (OH), 3320 (≡CH), 1720 cm^{-1} (ester C=O); nmr (CCl_4) δ 2.38 (t, 1, J = 2.5 Hz, C≡CH), 3.76 (s, 3, MeO at C-4), 3.82 (s, 6, 2 MeO), overlapping broadened band at *ca.* 3.8 (H_2O?), 4.71 (d, 2, CH_2), 6.73 (s, 2, H-2 and H-6).

Anal. Calcd for $C_{15}H_{14}O_5 \cdot 0.25H_2O$: C, 64.63; H, 5.24; O, 30.13. Found: C, 64.98; H, 5.12; O, 30.40.

3-Hydroxymethyl-2-naphthoic Acid Lactone (1b). (a) From Ester 9.—A solution of 1.42 g of $9 \cdot 0.25H_2O$ in 80 ml of Ac_2O was refluxed in a nitrogen atmosphere for 48 hr and then evaporated to dryness. Addition of MeOH to the residue gave 0.19 g (14%) of white plates, mp 202–206°, raised to 203.5–205° (lit.[15] 206°) on recrystallization from acetone–MeOH: ir ($CHCl_3$) 1760 cm^{-1} (γ-lactone); nmr ($CDCl_3$, HA-100) δ 5.48 (s, 2, CH_2), 7.26 (s, 1, H-4), 7.4–7.8 (m, 2, H-6 and H-7), 7.8–8.2 (m, 2, H-5 and H-8), 8.50 (s, 1, H-1).

Anal. Calcd for $C_{12}H_8O_2$: C, 78.15; H, 4.52. Found: C, 78.25; H, 4.38.

(b) *Via* Phenylpropargyl Propiolate (3).—A mixture of 0.81 g (8.8 mmol) of sodium propiolate, 1.32 g (8.8 mmol) of phenylpropargyl chloride, and 15 ml of dimethylformamide was refluxed for *only* 30 min in a nitrogen atmosphere and then evaporated to dryness. The residue was treated with CCl_4, filtered to remove NaCl, and chromatographed by means of silica gel–benzene to give **3** as a liquid: yield 0.7 g (43%); ir (CCl_4) 3320 (≡CH), 2130 (C≡C), 1730 cm^{-1} (ester C=O); nmr (CCl_4) δ 2.86 (s, 1, C≡CH), 4.95 (s, 2, CH_2), 7.1–7.6 (m, 5, phenyl).

Refluxing the crude **3** in Ac_2O gave a mixture of products from which was isolated 11 mg (2%) of **1b**, mp 204–205.5°, identified by direct comparison with product from method a.

3-Hydroxymethyl-3,4-dihydro-2-naphthoic Acid Lactone (17).—As in the preparation of ester **3**, equimolar quantities of sodium propiolate and *trans*-cinnamyl chloride (Eastman Kodak) gave, on chromatography, a crude product, purified further by evaporative distillation at 70–80° (0.1 mm) to give colorless, liquid ***trans*-cinnamyl propiolate (6)** (19%): ir (CCl_4) 3320 (≡CH), 2160 (C≡C), 1710 (ester C=O), 960 cm^{-1} (*trans*-CH=CH); nmr (CCl_4) δ 2.83 (s, 1, C≡CH), 4.67 (d, 2, J = 6 Hz, CH_2), 6.09 (d of t, 1, J_{trans} = 16 Hz, CH=CHCH$_2$), 6.59 (d, 1, CH=CHCH$_2$), 7.1–7.5 (broad s, 5, phenyl).

A solution of 2.6 g of **6** in 100 ml of Ac_2O was refluxed in a nitrogen atmosphere for 3 days and then evaporated. Extraction of the residue with boiling hexane, followed by concentration of solvent, addition of benzene (10% by vol), and cooling gave 0.21 g (8%) of **17**, obtained as a cream-colored powder: mp 136–138°, raised to 139–140° on recrystallization; ir ($CHCl_3$) 1760 cm^{-1} (γ-lactone); nmr ($CDCl_3$) δ 2.2–3.7 (m, 3, CH_2CHCH_2O), 4.04 and 4.78 (2 pseudotriplets, 1 each, CH_2O), 7.1–7.6 (m, 5, H-1 and aromatic H); mass spectrum[16] *m/e* at 186 (62), 156 (42), 155 (21), 142 (22), 141 (13), 129 (17), 128 (100), 127 (21), 63 (12), 51 (11), metastable peaks at 154, 131, 105, 104.

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.46; H, 5.41.

The nmr spectrum of **17** shows the same pattern of signals for aliphatic protons as found in 1-phenyl-3-hydroxymethyl-3,4-dihydro-2-naphthoic acid lactone.[4] The major fragments lost from electron impact on **17** are CH_2O, CO_2, CO, and H. The most abundant peak (*m/e* 128) corresponds to a naphthalene cation radical.

6,7-Methylenedioxy-3-hydroxymethyl-2-naphthoic Acid Lactone (15). (a) *Via* Enynic Ester.—An equimolar mixture of sodium 3,4-methylenedioxycinnamyl alkoxide[7] and propiolyl chloride in benzene was stirred for 3 hr, refluxed for 40 min, washed with water, and evaporated to dryness to give crude liquid ***trans*-3,4-methylenedioxycinnamyl propiolate (7)** (40%): ir ($CHCl_3$) 3320 (≡CH), 2270 (C≡C), 1730 (ester C=O), 940 cm^{-1} (OCH_2O);[14] nmr (CCl_4) δ 2.76 (s, C≡CH), 4.75 (d, J = 6 Hz, CH_2OC=O), 5.95 (s, OCH_2O), 6.0–7.0 (aromatic and vinylic H).

Refluxing this ester with Ac_2O, evaporation of the solvent, and treatment of the residue with petroleum ether gave crystals of **15**, mp 280–282° (13%), converted to a light yellow solid (mp 282–283°) on recrystallization from benzene–petroleum ether, CCl_4, and $CHCl_3$ plus sublimation at 0.5 mm: ir ($CHCl_3$) 1760 (γ-lactone), 930 cm^{-1} (OCH_2O); nmr ($CDCl_3$, HA-100) δ 5.42 (s, lactone CH_2), 6.12 (s, OCH_2O), 7.19 and 7.69 (2 s, H-4, H-5, H-8), 8.28 (s, H-1).

Anal. Calcd for $C_{13}H_8O_4$: C, 68.42; H, 3.53. Found: C, 68.76; H, 3.78.

(b) *Via* Diynic Ester.—Part a was repeated but with sodium 3,4-methylenedioxyphenylpropargyl alkoxide as the salt. A sample of the crude intermediate liquid **3,4-methylenedioxyphenylpropargyl propiolate (4)** showed an ir spectrum ($CHCl_3$): 3320 (≡CH), 2130 (C≡C), 1730 (ester C=O), 940 cm^{-1} (OCH_2O).[14] The overall yield of lactone **15** was 3%, mp 280–282°, identical with compound in method a as based on mixture melting point, as well as ir and nmr spectra.

6,8-Dimethoxy-3-hydroxymethyl-2-naphthoic Acid Lactone

(14) L. H. Briggs, L. D. Colebrook, H. M. Fales, and W. C. Wildman, *Anal. Chem.*, **29**, 904 (1957).

(15) F. Mayer, W. Schaefer, and J. Rosenbasch, *Arch. Pharm.* (*Weinheim*), **267**, 571 (1929); *Chem. Abstr.*, **24**, 839 (1930).

(16) Stable peaks of relative abundance less than 10% are not reported.

(16). (a) *Via* **Enynic Ester.**—In the foregoing manner was prepared the crude liquid ester *trans*-**3,5-dimethoxycinnamyl propiolate** (**8**): nmr ($CDCl_3$) δ 2.92 (s, C≡CH), 3.76 (s, 2 MeO), 4.80 (d, J = 6 Hz, CH_2), 6.2–6.7 (m, aromatic and vinylic H). Refluxing this ester in Ac_2O gave lactone **16**, mp 201–210° (5% overall). Sublimation at 0.5 mm raised the melting point to 212.5–214°.

(b) *Via* **Diynic Ester.**—Likewise was obtained the crude liquid ester **3,5-dimethoxyphenylpropargyl propiolate** (**5**): ir (CCl_4) 3320 (≡CH), 2130 (C≡C), 1720 cm^{-1} (ester C=O); nmr (CCl_4) δ 2.91 (s, C≡CH), 3.77 (s, 2 MeO), 4.25 (s, CH_2), 6.2–6.6 (m, aromatic H). Cyclization was effected in 10% yield to give lactone **16**: mp 201.5–204.5°, raised to 212.5–214° on recrystallization from benzene–petroleum ether plus sublimation at 0.5 mm; ir ($CHCl_3$) 1760 cm^{-1} (γ-lactone); nmr ($CDCl_3$, HA-100) δ 3.96 and 4.01 (2 s, 3 each, 2 MeO), 5.41 (s, 2, CH_2), 6.54 and 6.77 (2 d, 1 each, J_m = 2.5 Hz, H-5 and H-7), 7.64 (slightly split s, 1, H-4), 8.81 (s, 1, H-1); identical with product from method a as based on mixture melting point, as well as ir and nmr spectra.

Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 69.06; H, 5.18.

Registry No.—**1b**, 4711-50-6; **3**, 29577-27-3; **4**, 29577-28-4; **5**, 29577-29-5; **6**, 29584-68-7; **7**, 29584-61-0; **8**, 29584-62-1; **9**, 29577-30-8; **10**, 29577-31-9; **11**, 29577-32-0; **12**, 29577-33-1; **13**, 29584-63-2; **14**, 29577-34-2; **15**, 5656-51-9; **16**, 29577-36-4; **17**, 29577-37-5; **18**, 29577-38-6; phenylpropargyl chloride, 3355-31-5; ethyl *trans*-3,5-dimethoxycinnamate, 29584-64-3; methyl *trans*-3,5-dimethoxycinnamate, 29584-65-4; *trans*-3,5-dimethoxycinnamyl alcohol, 29584-66-5; 3-(3,5-dimethoxyphenyl)-1-propanol, 1080-05-3; ethyl *trans*-2-bromo-3,5-dimethoxycinnamate, 29641-89-2; *trans*-2-bromo-3,5-dimethoxycinnamic acid, 29584-67-6; 3,5-dimethoxyphenylpropargyl alcohol 29577-41-1.

Electrolyte and Micellar Effects on Meisenheimer Complex Equilibria[1,2]

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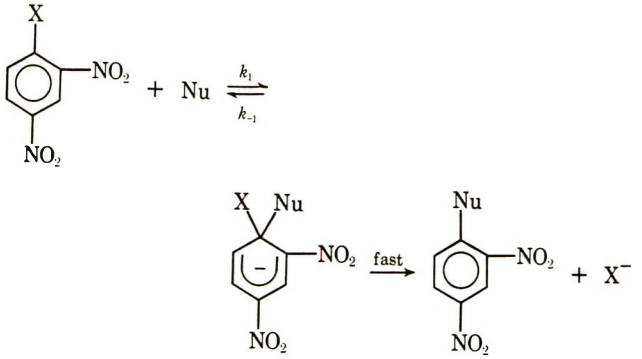
Electrolytes, with the exception of lithium salts, decrease the rate constant for the decomposition of sodium 1,1-dimethoxy-2,4,6-trinitrocyclohexadienylide (**1**) in aqueous solutions. Cationic micellar CTAB and nonionic micellar Igepal CO-730 also decrease the decomposition rate of **1** by factors of 12 and 3.7, respectively, and anionic NaLS does not affect it. Both enthalpy and entropy factors are involved. The magnitude of micellar rate retardation is smaller for 1,1-dimethoxy-2,4-dinitro- (**2**) and 1,1-dimethoxy-2,4,5-trinitronaphthalene (**3**) complexes but is significantly greater for the spiro Meisenheimer complex of 1-(β-hydroxyethoxy)-2,4-dinitronaphthalene (**5**) than for **1**. The electrolyte and micellar effects originate from less destabilization of the initial state than of the transition state. CTAB enhances the equilibrium constants for the formation of the spiro complex of 1-(β-hydroxyethoxy)-2,4,6-trinitrobenzene and **5** by factors of 4750 and 250, respectively, while NaLS or Igepal have no appreciable effects. These results are compared critically to those obtained for other nucleophilic aromatic substitutions.

The effects of electrolytes and micelles on the reactions between nucleophiles and 2,4-dinitrohalobenzenes have been determined in aqueous solutions.[4] Such nucleophilic aromatic substitutions involve the rate-determining formation of an intermediate which decomposes rapidly to products. The relative effects



of electrolytes on the rate constants for the reaction of hydroxide ion with 2,4-dinitrochlorobenzene, for example, are $Me_4NCl > K_2SO_4 > Na_2SO_4 > KCl \sim H_2O > NaCl > NaBr \sim NaNO_3 > Li_2SO_4 > LiCl > LiBr > CH_3C_6H_4SO_3Na > LiClO_4$.[4] These electrolyte effects have been dissected into those on the activity coefficient of the aryl halide and those on the ratio of the activity coefficient of the hydroxide ion to that of the transition state. KCl, NaCl, NaBr, and LiBr increase f_{ArX} but decrease $f_{OH^-}/f^{\pm}$; $NaClO_4$, on the other hand, decreases both f_{ArX} and $f_{OH^-}/f^{\pm}$.

Cationic micellar surfactants were found to enhance k_1 by factors of *ca.* 60–80, the magnitude of the rate decrease by anionic surfactants was somewhat more modest, and neutral micellar surfactants had no effect on k_1.[4,5]

In order to obtain information on the effects of electrolytes and micelles on nucleophilic aromatic substitutions in which the rate-determining step is governed by the decomposition of the complex, we have investigated these effects on the rates of decomposition of sodium 1,1-dimethoxy-2,4,6-trinitrocyclohexadienylide (**1**). Since micellar catalysis involves specific substrate–micelle interactions, we have also examined the influence of micellar surfactants on the rates of decomposition of the methoxyl complexes of 1-methoxy-2,4-dinitronaphthalene (**2**) and 1-methoxy-2,4,5-trinitronaphthalene (**3**) and of the spiro Meisenheimer

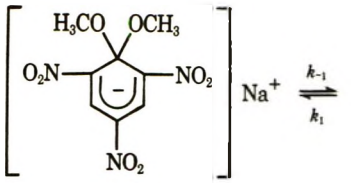
(1) Supported in part by the U. S. Atomic Energy Commission.

(2) Reported, in part, preliminarily by E. J. Fendler and J. H. Fendler, *Chem. Commun.*, 816 (1970).

(3) (a) Texas A & M University; (b) Department of Chemistry, Franklin and Marshall College, Lancaster, Pa. 17604.

(4) C. A. Bunton and L. Robinson, *J. Amer. Chem. Soc.*, **90**, 5965, 5972 (1968); C. A. Bunton and L. Robinson, *J. Org. Chem.*, **34**, 780 (1969); C. A. Bunton and L. Robinson, *ibid.*, **35**, 733 (1970); C. A. Bunton and L. Robinson, *J. Amer. Chem. Soc.*, **92**, 356 (1970).

(5) For reviews of micellar effects on reaction rates, see E. H. Cordes and R. B. Dunlap, *Accounts Chem. Res.*, **2**, 329 (1969), and E. J. Fendler and J. H. Fendler, *Advan. Phys. Org. Chem.*, **8**, 271 (1970).



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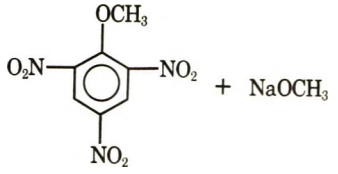
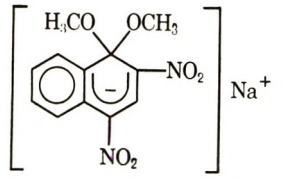


complexes **4** and **5**. Micellar effects on the equilibrium constants for the formation of complexes **4** and **5** from their parent glycol ethers, 1-(β-hydroxyethoxy)-



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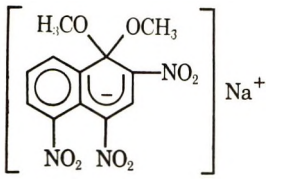

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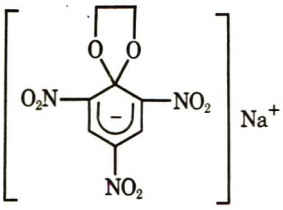

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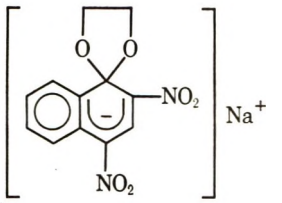

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2,4,6-trinitrobenzene (**6**) and 1-(β-hydroxyethoxy)-2,4-dinitronaphthalene (**7**), have also been determined.

Experimnetal Section

The preparations of 1-(β-hydroxyethoxy)-2,4,6-trinitrobenzene (**6**),[6] 1-(β-hydroxyethoxy)-2,4-dinitronaphthalene (**7**),[6] their spiro Meisenheimer complexes **4**[6] and **5**,[6] and the methoxyl complexes of 2,4,6-trinitroanisole (**1**),[7] 1-methoxy-2,4-dinitronaphthalene (**2**),[8] and 1-methoxy-2,4,5-trinitronaphthalene (**3**)[9] have been described. Reagent grade salts were dried *in vacuo* over phosphorus pentoxide immediately prior to their use in making up the electrolyte solutions. The sources of the surfactants and their purification have been described previously.[10] The buffer, electrolyte, and surfactant solutions were prepared in deionized distilled water. The pH's of the solutions were adjusted using HCl or NaOH to the required value and were measured at 25.0° with an Orion-801 pH meter. Both in the case of the decomposition of complexes **1**–**3** and in the determinations of the equilibrium constants for the formation of complexes **4** and **5** in micellar solutions, the pH remained within ±0.02 during the experiments.

Four solubility determinations were carried out for each solvent system; saturated solutions of **1**, **2**, and **5** containing undissolved solid were shaken at 25.00° and filtered, and the concentration of complex **1**, **2**, or **5** in the filtrate was determined spectrophotometrically. The error in the individual measurements is ±10%. In some cases, the complex concentration in the saturated solutions was greater than 1.0 *M* and thus is not ideal.

The required absorbance measurements were carried out at the appropriate wavelength[6-9] in the thermostated cell compartment of a Beckman DU-2 spectrophotometer. The temperature was measured inside the cells and was maintained within ±0.02°. The decomposition of the complexes obeyed good first-order kinetics.

Results

In aqueous solution, the decomposition of Meisenheimer complexes is pH independent in solutions more alkaline than pH 8.0.[6-9] All of the present investigations, unless stated otherwise, have been carried out in the middle of the plateau of the pH-rate profile, *i.e.*, in the pH-independent region at pH 10.8.

Electrolytes have significant effects on the rate of decomposition of Meisenheimer complex **1** (Table I).

TABLE I

ELECTROLYTE EFFECTS ON THE DECOMPOSITION RATES OF 1,1-DIMETHOXY-2,4,6-TRINITROCYCLOHEXADIENYLIDE ION (1) IN WATER AT 25.00°[a]

Electrolyte	10^4k_{-1}, sec^{-1} 1.0 *M*	2.0 *M*
None	5.08[b]	
$LiClO_4$	6.51	7.43
LiCl	5.98	6.19
$NaNO_3$	4.25	3.54
NaCl	4.16	3.33
NaBr	4.21	3.33
Me_4NCl	4.12	2.68
$NaClO_4$	3.98	2.97
KCl	3.63	2.56
Na_2SO_4	3.45	2.30
p-$MeC_6H_4SO_3Na$	2.64	1.18

[a] At pH = 10.8. [b] Mean of six runs, each within ±3%.

With the exception of lithium perchlorate and lithium chloride, all the electrolytes decrease the rate constants for the decomposition of **1**. Results of the solubility measurements, expressed as activity coefficients relative to water containing 10^{-3} *M* sodium hydroxide at 25.00°, show that all the electrolytes investigated substantially affect the activity coefficients of **1** (Table II).

TABLE II

ELECTROLYTE EFFECTS ON THE RELATIVE ACTIVITY COEFFICIENTS OF SODIUM 1,1-DIMETHOXY-2,4,6-TRINITROCYCLOHEXADIENYLIDE (1) AND ON ITS DECOMPOSITION TRANSITION STATE AT 25.00°

Electrolyte	1.0 *M* Electrolyte $f_1^s/f_1^{o\,a}$	1.0 *M* Electrolyte $f^{s\ddagger}/f^{o\ddagger\,b}$	2.0 *M* Electrolyte $f_1^s/f_1^{o\,a}$	2.0 *M* Electrolyte $f^{s\ddagger}/f^{o\ddagger\,b}$
$LiClO_4$	0.81	0.633	1.06	0.726
LiCl	1.03	0.873	2.98	2.44
p-$MeC_6H_4SO_3Na$	3.04	5.84	1.74	7.49
$NaClO_4$	4.60	5.87	5.93	10.1
$NaNO_3$	6.18	7.33	10.5	15.0
NaBr	8.95	10.8	13.7	20.9
NaCl	9.08	11.1	19.5	29.7
Me_4NCl	13.0	16.0	27.8	52.7
Na_2SO_4	20.6	30.3	74.1	165
KCl	37.3	52.2	45.8	90.9

[a] Relative activity coefficients for **1**. [b] Relative activity coefficient for the transition state for the formation of 2,4,6-trinitroanisole.

Cationic and neutral micellar surfactants decrease the rate constants for the pH-independent decom-

(6) E. J. Fendler, J. H. Fendler, W. E. Byrne, and C. E. Griffin, *J. Org. Chem.*, **33**, 4144 (1968).
(7) J. H. Fendler, E. J. Fendler, and C. E. Griffin, *ibid.*, **34**, 689 (1969).
(8) J. H. Fendler, E. J. Fendler, W. E. Byrne, and C. E. Griffin, *ibid.*, **33**, 977 (1968).
(9) J. H. Fendler and E. J. Fendler, *ibid.*, **35**, 3378 (1970).
(10) E. J. Fendler, R. R. Liechti, and J. H. Fendler, *ibid.*, **35**, 1658 (1970).

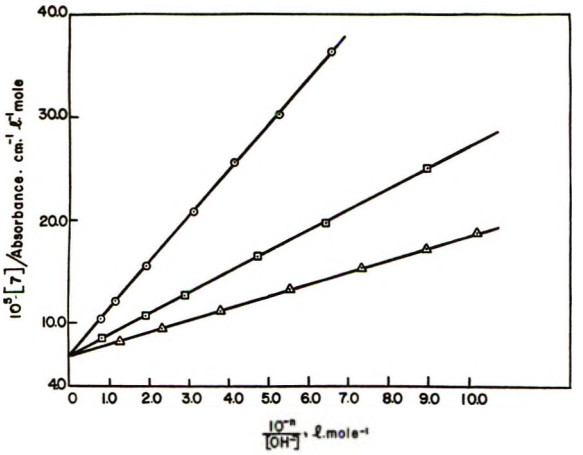


Figure 1.—Benesi–Hildebrand plots for the formation of **5** in water at 25.00°: ⊙ 1.0×10^{-2} *M* CTAB, $n = 7$; ⊡ 1.0×10^{-2} *M* NaLS, $n = 4$; △ water, $n = 4$.

positions of complexes **1**, **2**, **3**, and **5**, but anionic NaLS has no effect on these rates (Table III). Table IV gives the relative solubilities, and hence the activity coefficients, of complexes **1**, **2**, and **5** in micellar CTAB and NaLS solutions. We have examined the effects of micelles on the acid-catalyzed decomposition of complex **3**. The second-order rate constants for the acid-catalyzed decomposition of **3** at 25.00° in water, 2.0×10^{-2} *M* NaLS, and 1.0×10^{-2} *M* CTAB in the pH range 4.0–6.4 (5.0×10^{-3} *M* KH_2PO_4 and CH_3CO_2Na buffers) are 1380, 2833 and 41 l. mol^{-1} sec^{-1}, respectively.

The effects of micelles on the energies and entropies of activation for the pH-independent decomposition of complex **1** are given in Table V.

TABLE III

MICELLAR EFFECTS ON THE DECOMPOSITION RATES OF MEISENHEIMER COMPLEXES IN WATER AT 25.00°[a]

Complex	10^5k_{-1}, sec^{-1}, in H_2O	10^5k_{-1}, sec^{-1}, in CTAB	10^5k_{-1}, sec^{-1}, in NaLS	10^5k_{-1}, sec^{-1}, in Igepal
		4.20[b]		13.6[e]
1	50.8	5.20[c]	52.0[d]	12.3[f]
				7.45[g]
2	176	58.6[b]	178[b]	
3	16.0	8.32[b]	17.0[d]	
5	138	0.21[h]	158[d]	4.2[e]

[a] At pH 10.8. [b] 2.5×10^{-2} *M* CTAB. [c] 2.0×10^{-3} *M* CTAB. [d] 1.0×10^{-1} *M* NaLS. [e] 1.0×10^{-2} *M* Igepal CO-730. [f] 2.0×10^{-2} *M* Igepal DM-730. [g] 2.5×10^{-2} *M* Igepal CO-850. [h] 1.0×10^{-2} *M* CTAB.

TABLE IV

MICELLAR EFFECTS ON THE RELATIVE ACTIVITY COEFFICIENTS OF COMPLEXES 1, 2, AND 5 AND ON THEIR DECOMPOSITION TRANSITION STATES

Complex	2.5×10^{-2} *M* CTAB f^m/f^o[a]	2.5×10^{-2} *M* CTAB $f^{m\ddagger}/f^{o\ddagger}$[a]	1.0×10^{-1} *M* NaLS f^m/f^o[a]	1.0×10^{-1} *M* NaLS $f^{m\ddagger}/f^{o\ddagger}$[a]
1	0.65	7.9	0.65	0.63
2	1.01	3.1	1.01	0.99
5	1.04	665	0.97	0.85

[a] f^m, f^o, $f^{m\ddagger}$ and $f^{o\ddagger}$ are the activity coefficients of complexes **1**, **2**, and **5** in micellar surfactant solutions, in water, and that of their decomposition transition states in the presence of micelles and in water, respectively.

TABLE V

ARRHENIUS PARAMETERS FOR THE DECOMPOSITION OF 1,1-DIMETHOXY-2,4,6-TRINITROCYCLOHEXADIENYLIDE ION (1) IN MICELLAR SOLUTIONS[a]

Media	E_{-1} kcal/mol[b]	$\Delta S_{-1}^{\ddagger}$, eu,[b] at 25.00°
Water	17.6 ± 0.8	−16.5 ± 2.0
2.5×10^{-2} *M* CTAB	24.9 ± 0.8	+3.1 ± 2.0
1.0×10^{-2} Igepal CO-730	20.5 ± 0.8	−9.6 ± 2.0

[a] pH 10.8. [b] Calculated from linear Arrhenius plots obtained from runs at 25.00°, 30.25°, and 35.00°.

Although complexes **4** and **5** are formed from **6** and **7** in aqueous alkaline solutions,[4,11] the rate of their equilibrium attainment is immeasurably fast by our technique.[7] Using the Benesi–Hildebrand equation[12]

$$\frac{[6] \text{ or } [7]}{A} = \frac{1}{\epsilon} + \frac{1}{K\epsilon}\left(\frac{1}{[OH^-]}\right)$$

where A is the absorbance in a 1.0-cm cell, ϵ is the molar extinction coefficient, and K is the equilibrium constant for the formation of complex **4** or **5**, good linear relationships were obtained on plotting $[6]/A$ or $[7]/A$ *vs.* $1/[OH^-]$ (Figure 1) indicating that simple equilibria prevail. Since the intercept of the Benesi–Hildebrand plot (*i.e.*, $1/\epsilon$) is susceptible to large errors, previously obtained[6] values of ϵ have been used to determine the K values. The determined values for the equilibrium constants for the formation of **4** and **5** in water and in micellar surfactant solutions at 25.00° are given in Table VI.

TABLE VI

MICELLAR EFFECTS ON THE EQUILIBRIUM CONSTANTS FOR THE FORMATION OF MEISENHEIMER COMPLEXES AT 25.00°[a]

Complex	K, l. mol^{-1}, in H_2O	K, l. mol^{-1}, in CTAB	K, l. mol^{-1}, in NaLS	K, l. mol^{-1}, in Igepal
4	2.1×10^7	1.0×10^{11}[b]		
5	5.82×10^4	1.47×10^7[b]	3.20×10^4[c]	6.8×10^4[d]

[a] Determined from linear Benesi–Hildebrand plots (see Figure 1 for typical plots). [b] 1.0×10^{-2} *M* CTAB. [c] 1.0×10^{-2} *M* NaLS. [d] 1.0×10^{-2} *M* Igepal CO-730.

Discussion

Effects of Electrolytes.—Lithium perchlorate and lithium chloride enhance whereas all the other electrolytes investigated retard the rate of decomposition of the methoxyl complex of 2,4,6-trinitroanisole (**1**). Simple electrostatic theory[13] clearly fails to account for both the direction and the magnitude of these effects. The order of the electrolyte effects on k_{-1}, $LiClO_4 > LiCl > H_2O > NaNO_3 > NaCl > NaBr > Me_4NCl > NaClO_4 > KCl > Na_2SO_4 > p\text{-}MeC_6H_4SO_3Na$ (Table I), is essentially the reverse of that found for the interaction of hydroxide ion with 2,4-dinitrochlorobenzene.[4]

These electrolytes also have substantial effects on the mean ion activity coefficient ratios of sodium 1,1-dimethoxy-2,4,6-trinitrocyclohexadienylide (**1**). With

(11) J. Murto, *Suom. Kemistilehti*, *B*, **38**, 255 (1965).
(12) H. A. Benesi and J. H. Hildebrand, *J. Amer. Chem. Soc.*, **71**, 2703 (1949).
(13) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed., Cornell University Press, Ithaca, N. Y., 1969.

the exception of lithium perchlorate, all the salts increase the mean ion activity coefficient of **1** (Table II). In the 0–2.0 *M* electrolyte concentration range, the logarithms of the mean ion activity coefficient ratios do not vary linearly as a function of concentration; *i.e.*, the Setschenow equation is not obeyed. Since the extent of the changes in the activity coefficients of the single anion, 1,1-dimethoxy-2,4,6-trinitrocyclohexadienylide ion, and its sodium counterion are not known, this behavior is not unexpected. The observed order of the activity coefficient ratios for **1**, $LiClO_4$ < LiCl < *p*-$MeC_6H_3SO_3Na$ < $NaClO_4$ < $NaNO_3$ < NaBr < NaCl < Me_4NCl < Na_2SO_4 < KCl, does not follow any particular trend. It is worth noting, however, that the effects of electrolytes on the mean ion activity coefficients of **1** are significantly greater than those on the activity coefficients of 2,4-dinitrochlorobenzene.[4] Furthermore, electrolytes with the exception of NaCl, LiCl, and Na_2SO_4 stabilize, *i.e.*, decrease the activity coefficient of 2,4-dinitrochlorobenzene, whereas they primarily destabilize complex **1**. The observed rate constant changes in the presence of electrolytes are therefore due partially to initial state effects. The magnitude of the electrolyte effects on the transition state can be determined by means of the Brønsted–Bjerrum rate equation

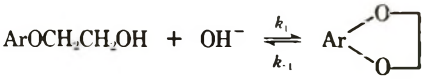
$$k_{-1}^{s} = k_{-1}^{o} \frac{f_1}{f^{\pm}}$$

where k_{-1}^{s} and k_{-1}^{o} are the rate constants for the decomposition of **1** in the presence and absence of electrolytes and f_1 and $f^{\pm}$ are relative mean ion activity coefficients for **1** and for its decomposition transition state. Since electrolyte effects have been obtained both on k_{-1} and on the mean ion activity coefficient ratios of **1**, substitution into the Brønsted–Bjerrum rate equation allows the determination of the effects of electrolytes on the transition state for the decomposition of **1** (see Table II). Electrolytes, with the exception of lithium salts, destabilize both **1** and its decomposition transition state. More significantly, their effects are considerably more pronounced on the transition state than on the initial state. The results of the present study clearly illustrate the inherent complications of kinetic salt effects even on relatively simple reactions.

Micellar Effects.—Cationic and nonionic micelles retard the pH-independent decomposition of Meisenheimer complexes, while anionic NaLS has no appreciable affect on the rate (Table III). As in the case of the electrolyte effects, the direction of the micellar effects on the rate of decomposition of the complexes is opposite to that found for the interaction of nucleophiles with dinitro-substituted halobenzenes,[4] in which case the rate-determining step is the formation rather than the decomposition of the σ complex. Since the rate constants for the decomposition of **1** are decreased only by a factor of *ca.* 2 in the presence of 1.0–2.0 *M* trimethylammonium chloride and sodium *p*-toluenesulfonate while the addition of 10^{-2} *M* CTAB results in a 12-fold rate retardation, the latter affects are clearly not electrolytic but micellar in origin.

The magnitude of the micellar effects is markedly dependent upon the nature of the substrate. CTAB retards the decomposition of **1**, **2**, **3**, and **5** by factors of 12, 3, 2, and 660, respectively. This substrate specificity and the catalytic behavior in micellar solutions must result from differences in initial state or in transition state stabilities, *i.e.*, activities, or, indeed, from a combination of both, relative to those in water. In order to distinguish between these alternatives, we have calculated the activity coefficient ratios for complexes **1**, **2**, and **5** in CTAB and NaLS relative to water from solubility measurements (Table IV). Unlike the electrolytes (Table II), the micelles generally have only small or insignificant effects on the activity coefficients of these complexes. Complex **1** is solubilized to some extent by CTAB and NaLS, whereas the initial state activities of complexes **2** and **5** are not affected by these micelles. The micellar effects of CTAB and NaLS on both the rate of decomposition, k_{-1}, and the initial state stability of complex **1** parallel that found in water–DMSO solutions as a function of increasing concentration of the dipolar aprotic component.[14] Combination of the rate constant data with the relative activity coefficients of complexes **1**, **2**, and **5** in the micellar surfactant solutions affords an estimation of the effects of CTAB and NaLS on the activity coefficients for the decomposition of these complexes (Table IV). It is apparent that the retardation of the rates of decomposition of the complexes in the presence of micellar CTAB is primarily the consequence of destabilization of the transition state, whereas the absence of catalysis by NaLS results from compensation of initial and transition state effects in the case of complex **1** and from insignificant differences for complexes **2** and **5**. The retardation of the rate of decomposition of **1** is, as has been observed in many other micellar catalyses,[5] a composite of both enthalpy and entropy effects (Table V). These results suggest that the transition state for complex decomposition is further along the reaction coordinate in water than in micellar CTAB.

The equilibrium constants for the formation of spiro Meisenheimer complexes in methanol are considerably greater than those of their 1,1-dialkoxy analogs.[6] Indeed, the dialkoxy Meisenheimer complexes have not been observed in water, whereas the spiro complexes **4** and **5** are quite stable (Table VI). The mechanism for the formation of complexes **4** and **5** can be described in terms of an initial rapid proton abstraction from the glycol ether, **6** or **7**, by hydroxide ion followed by rate-determining internal cyclization of the resulting glycolate ion. The rigidity of the cyclic substituent perpendicular to the benzene ring is responsible for the enhanced stabilities of these complexes.[6] The dramatic 660-fold decrease in the rate of decomposition of the spiro complex **5** as compared to the threefold rate retardation for the 1,1-dialkoxy analog **2** by micellar CTAB is explicable exclusively in terms of transition state effects (Table IV). The rate retardation by nonionic Igepal CO-730 is also significant, whereas sodium dodecyl sulfate has no discernable affect on the rate of decomposition of **5** (Table III). The equilibrium constants ($K = k_1/k_{-1}$) for the formation of spiro σ complexes (as illustrated below) in the



(14) J. H. Fendler and J. W. Larsen, *J. Amer. Chem. Soc.*, in press.

presence and in the absence of micellar surfactants have also been determined (Table VI). Cationic micellar CTAB enhances the equilibrium constant for the formation of **4** and **5** by factors of 4750 and 252, respectively, while NaLS and Igepal do not affect it. Since the rate constants for the formation of spiro complexes, k_1, are dependent on the hydroxide ion concentration, the observed micellar effects are composites of those on the parent glycol ethers **6** and **7** and those on the hydroxide ion. The effective hydrogen ion concentration at the micellar surface, however, may differ appreciably from that in the bulk phase.[5] The considerably more pronounced micellar effect on the rate of the acid-catalyzed decomposition of **1** than that on its neutral decomposition substantiate this observation. The interpretation of this and similar results in buffered solutions is complicated by the uncertainties in the pH of these solutions.[5] Combination of the values for k_{-1} and K for the spiro complex **5** in the absence and presence of CTAB (Tables III and VI) allows the calculation of the rate constants for the formation of **5** ($k_1^{H_2O}$ = 80 l. mol^{-1} sec^{-1}, k_1^{CTAB} = 31 l. mol^{-1} sec^{-1}). Micellar CTAB thus decreases the rate constant for the formation of **5** by a factor of 2.6, whereas it catalyzes the hydroxydehalogenations of dinitrosubstituted arenes by factors of *ca.* 60–80.[4] These micellar effects are not unexpected based on electrostatic considerations since the rate of the former reaction, which involves the internal cyclization of the naphthyl glycolate anion, would predictably be retarded in the presence of cationic micelles due to partial charge neutralization. The latter case, however, is a typical example of the effect of cationic micelles on a reaction between a solubilized neutral organic molecule and a small high-charge density anion.[4,5] The unusually large increase in the equilibrium constant for the formation of **5** is, of course, the consequence of the micellar enhancement of the rate of formation, k_1, and the micellar retardation of the rate of decomposition. Combining k_{-1} and K values for the influence of Igepal CO-730 on complex **5**, one estimates that this nonionic surfactant somewhat unexpectedly decreases the rate constant for the formation of the complex. Qualitatively, the effects of ionic micelles on the rates of Meisenheimer complex decomposition are explicable in terms of simple electrostatic interactions, however the rate retardation caused by nonionic surfactants cannot be accounted for solely in simple electrostatic terms, and evnironmental effects, such as hydrophobic and hydrogen bonding interactions, must be invoked to rationalize the observed effects.

Although specific steric effects clearly complicate the interpretation of the results for the spiro complexes **4** and **5**, it is evident that micelles affect both the initial and transition states for the formation and the decomposition of intermediates which are involved in nucleophilic aromatic substitution and that this dependence is very much influenced by the nature of the substrates and intermediates.

Registry No.—**1**, 12275-58-0; **2**, 29472-26-2; **3**, 29472-29-5; **4**, 1280-24-6; **5**, 29472-28-4.

Ionic *vs.* Free-Radical Additions with Opportunity for Phenyl Migration. Solvent Effects[1]

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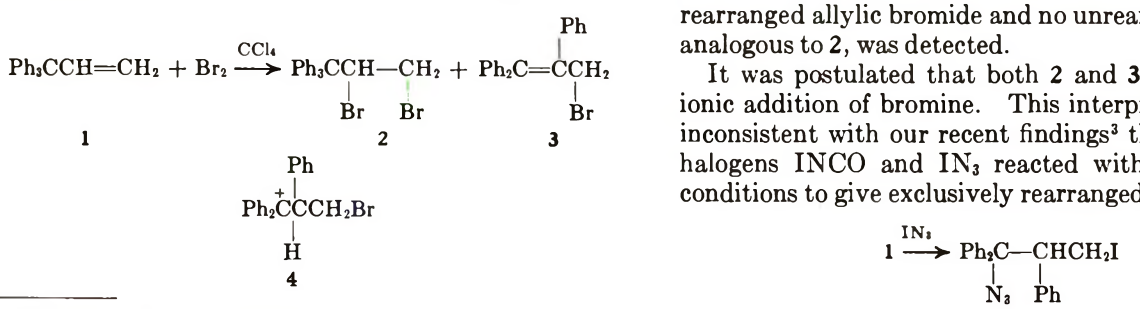
Addition of bromine azide to 3,3,3-triphenylpropene (**1**) proceeds with phenyl migration under ionic conditions (major product, **7**) but without phenyl migration under free-radical conditions (major product, **9**). The two products resulting from bromination of **1** were shown to derive from simultaneous ionic and free-radical addition processes. Addition of BrN_3 to 3,3-diphenylpropene (**10**) in polar solvents also proceeds with phenyl migration. The regiochemistry indicates steric control in the BrN_3 addition. Solvent effects of a different nature were observed during phenyl migration in the IN_3 addition to 3,3-diphenylpropene (**10**) and are interpreted in conjunction with three-membered-ring iodonium ion opening.

Recently Norman and coworkers[2] have shown that addition of bromine to 3,3,3-triphenylpropene (**1**) in carbon tetrachloride solution leads to a nonrearranged adduct **2** and an allyl bromide **3** in a ratio of 1:1.15. The unsaturated bromide **3** is a product of phenyl migration and probably arose from an intermediate of type **4** by loss of a proton. Norman, *et al.*, were in fact able to trap **4** by carrying out the bromination in methanol. 3-*p*-Anisyl-3,3-diphenylpropene, which reacts 25 times as fast as **1**, gave on bromination in CCl_4 only a rearranged allylic bromide and no unrearranged adduct, analogous to **2**, was detected.

It was postulated that both **2** and **3** result from an ionic addition of bromine. This interpretation seemed inconsistent with our recent findings[3] that the pseudohalogens INCO and IN_3 reacted with **1** under ionic conditions to give exclusively rearranged adducts (*cf.* **5**).



(1) Stereochemistry. LXI. For paper LX, see A. Hassner, *Accounts Chem. Res.*, **4**, 9 (1971).

(2) R. O. C. Norman and C. B. Thomas, *J. Chem. Soc. B*, 598 (1967).

(3) A. Hassner and J. S. Teeter, *J. Org. Chem.*, **35**, 3397 (1970).

At the same time we have shown[4] that bromine azide (BrN_3) in its additions to olefins is capable of both ionic and free-radical behavior, the latter being favored by solvents of low polarity. Hence, it became important to consider that bromine addition to **1** in CCl_4 may have proceeded by a dual mechanism, one leading to a rearranged, the other to a nonrearranged product.

Though the formation of the nonrearranged 1,2-dibromide **2** could be explained by fast trapping of an intermediate radical **6**, one cannot *a priori* assign the

$$Ph_3\dot{C}CHCH_2Br$$
6

formation of **2** to a free-radical addition since there are abundant examples in the literature[5] of phenyl migration to a β radical, for instance, eq 1.[5a]

$$Ph_3CCH_2\underset{\underset{O}{\|}}{C}H \xrightarrow[\Delta]{\text{peroxide,}} (Ph_3\dot{C}CH_2) + CO \qquad (1)$$
$$\downarrow$$
$$Ph_2CHCH_2Ph$$

Results and Discussion

1. Additions to Triphenylpropene.—The behavior of bromide azide with triphenylpropene **1** was examined first since, unlike for bromine, the regiochemistry[6] of the products should be helpful in establishing the reaction pathway. Addition of BrN_3 in nitromethane–methylene chloride purged with oxygen to inhibit free-radical reaction gave primarily (86%) the rearranged 1,3-bromoazide **7** and a small amount (6%) of 2,3,3-triphenylallyl bromide **3**. The structure of **7** was obvious

$$\underset{\mathbf{1}}{Ph_3CCH{=}CH_2} + BrN_3 \xrightarrow[\text{ionic}]{CH_3NO_2,} \underset{\underset{N_3}{|}}{\overset{\overset{Ph}{|}}{Ph_2CCHCH_2Br}} + \mathbf{3}$$
7

$$\downarrow \textit{tert}\text{-BuO}^- K^+, \text{ DMSO}$$

$$\underset{\underset{Ph\ \ O}{|\ \ \|}}{Ph_2C{=}C{-}CH}$$
8

from its nmr and mass spectra and from chemical reactions. Its nmr spectrum was very similar to that of the corresponding IN_3 adduct, including two aromatic peaks in a ratio of 13:2. The mass spectrum of **7** showed a base peak at *m/e* 180 ($Ph_2C{=}N^+$). A high-resolution mass spectrum confirmed the assignment of the base peak to a $C_{13}H_{10}N^+$ fragment. Like its iodo analog **5** bromo azide **7** was inert toward tertiary amines or potassium *tert*-butoxide in ether but was converted to triphenylacrolein **8** on treatment with potassium *tert*-butoxide in DMSO.

The formation of 6% of the allyl bromide **3** was unexpected since no corresponding product was found in the IN_3 addition to **1**; however, both **3** and **7** are the result of phenyl migration as expected from an ionic process.

(4) A. Hassner and F. Boerwinkle, *J. Amer. Chem. Soc.*, **90**, 216 (1968).

(5) (a) D. Y. Curtin and M. J. Hurwitz, *ibid.*, **74**, 5381 (1952); (b) S. Winstein and F. H. Senbold, *ibid.*, **75**, 2532 (1953); (c) P. D. Bartlett and J. D. Cotman, *ibid.*, **72**, 3095 (1950); L. H. Slaugh and J. H. Raley, *ibid.*, **82**, 1259 (1960); H. Meislich, J. Coustanza, and J. Streilitz, *J. Org. Chem.*, **33**, 3221 (1968).

(6) Regio is used to describe the directional effects in bond making or breaking: A. Hassner, *ibid.*, **33**, 2684 (1968).

The addition of BrN_3 to **1** in pentane in the presence of benzoyl peroxide and light proceeded much slower and led to the nonrearranged adduct **9** in 30% yield, in addition to 55% of unchanged olefin **1**.

$$\underset{\mathbf{1}}{Ph_3CCH{=}CH_2} + BrN_3 \xrightarrow[\text{(radical)}]{\text{pentane}} \underset{\underset{Br}{|}}{Ph_3CCHCH_2N_3}$$
9

$$Ph_3\dot{C}CHCH_2 \xrightarrow{BrN_3} \mathbf{9}$$
$$|$$
$$N_3$$
10

The structure of **9** was obvious from the base peak in its mass spectrum at *m/e* 243 (Ph_3C^+) as well as minor peaks at *m/e* 270 ($M\cdot^+ - BrN_3$) and 284 [$M\cdot^+ - (N_2 + Br)$]. The absence of products resulting from phenyl migration indicates that in the free-radical addition of BrN_3 an intermediate radical (*i.e.*, **10**) is trapped by bromine azide faster than it can rearrange.

Backed by these results we reexamined the addition of Br_2 to triphenylpropene **1** in CCl_4. The results shown in Table I clearly indicate that the 1,2-dibromide **2** is a

TABLE I

PRODUCTS IN THE BROMINATION OF 3,3,3-TRIPHENYLPROPENE IN CCl_4

Conditions	—Yield of products, %— 2	3
48 hr, room light[a]	45	55
46 hr, dark, O_2	11	73
46 hr, dark, O_2 2,6-Di-*tert*-butylphenol	0	88

[a] The procedure followed was that described in ref 2.

product of the free-radical addition of bromine to **1**, which is inhibited when the reaction is carried out in the presence of oxygen and of 2,6-di-*tert*-butylphenol. Hence, as in the case of BrN_3, ionic addition of Br_2 to **1** leads to phenyl migration, whereas free-radical addition produces an unrearranged adduct either instead of or in addition to rearranged product.

2. Additions to Diphenylpropene. Solvent Effects in Opening of Three-Membered-Ring Iodonium Ions.—We next turned our attention to 3,3-diphenylpropene (**10**) in which there is less crowding of phenyl groups than in **1**.

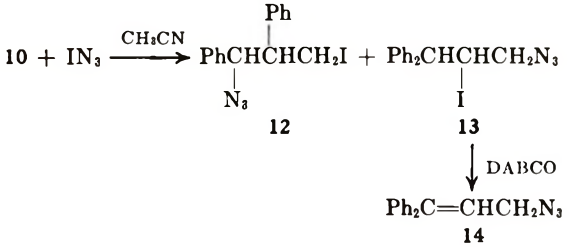
Several routes leading to 3,3-diphenylpropene (**10**) were investigated including the reported method of Walling, *et al.*[7] All led to a mixture of 1,1- and 3,3-diphenylpropene. The most satisfactory method proved to be a Wittig reaction on diphenylacetaldehyde followed by separation of the olefin isomers on $AgNO_3$–alumina. Addition of BrN_3, to **10** under ionic conditions proceeded with phenyl migration to produce in over 80% yield bromoazide **11**, the structure of which was assigned on the basis of its mass spectrum (base peak at *m/e* 104 for $PhCH{=}N^+$) and its low reactivity toward most bases or toward zinc (in analogy to **5** and **7**).

$$\underset{\underset{\mathbf{10}}{|}}{Ph_2\overset{H}{\overset{|}{C}}CH{=}CH_2} + BrN_3 \xrightarrow{CH_3NO_2} \underset{\underset{N_3}{|}}{Ph\overset{H\ Ph}{\overset{|\ \ |}{C}}CHCH_2Br}$$
11

(7) C. Walling and L. Bollyky, *ibid.*, **28**, 256 (1963).

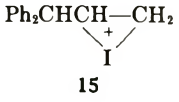
The formation of rearranged product **11** in good yield is indicative of the high propensity for phenyl migration even in the diphenyl system. Since in the monophenyl case (allylbenzene) no rearrangement was observed on IN_3 addition,[8] the presence of a phenyl substituent to stabilize the carbonium ion resulting from phenyl migration (*cf.* **4**) appears essential.

Interestingly, addition of IN_3 to **10** in acetonitrile gave rise to two iodo azide products that were separable by thick layer chromatography. The minor adduct was the expected phenyl rearrangement product **12** as indicated by the base peak in its mass spectrum at *m/e* 104 ($PhCH{=}N^+$). The major product was found to be the nonrearranged adduct **13**. By analogy with **9**,

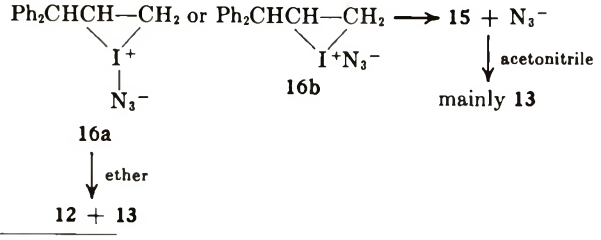


the base peak in the mass spectrum of **13** was at *m/e* 167 (Ph_2CH^+). The regiochemistry of **13** was proven by elimination of HI at 0° by means of 1,5-diazabicyclo-[4.3.0]-5-nonene or of 1,4-diazabicyclo[2.2.2]octane, which furnished the allyl azide **14**. The structure of **14** was obvious from its ir (strong azide absorption at 2112 cm^{-1}), nmr (triplet at τ 3.81 and doublet at τ 6.16), and uv spectrum [λ_{max} 253 nm (ϵ 14,500)].

Opening of the intermediate iodonium ion **15** at the terminal carbon to form **13** has evidently proceeded in a sterically controlled regiospecific manner as was reported for the IN_3 addition to *tert*-butylethylene.[8b]



Since IN_3 additions are generally ionic, the formation of both rearranged and nonrearranged adducts (**12** and **13**) was somewhat surprising. In order to determine whether adduct **13** was the result of a free-radical addition, we attempted to carry out the IN_3 addition in ether. This was possible by generation of IN_3 from silver azide (*caution!*) and ICl in ether. Although the reaction was slow in ether and *ca.* 20% of unreacted olefin **10** was recovered, we were able to obtain adducts **12** and **13** in 33% yield each. These results were not compatible with a free-radical pathway leading to **13**. We interpret the unusual solvent effect in the IN_3 addition to **10** in the following manner. In ether, a solvent of low polarity, the iodonium ion exists as a complex or a tight ion pair of type **16a** or **16b** which can undergo

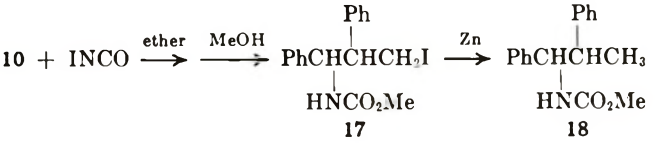


opening of the three-membered ring by phenyl migration to produce **12** or by attack of azide ion to form **13**. In a solvent of higher polarity, such as acetonitrile, dissociation of **16** into N_3^- and **15** takes place more readily and opening of **15** by azide ions competes more effectively with phenyl migration. To lend further support for this view, the IN_3 addition to **10** in ether was carried out in the presence of an excess of tetramethylammonium azide. As expected, the ratio of **13**:**12** increased considerably as shown in Table II.

TABLE II
SOLVENT EFFECTS ON PHENYL MIGRATION IN THE ADDITION OF IN_3 TO **10**

Solvent	Ratio of 13/12
Acetonitrile	6
Ether	1
Ether + $Me_4N^+N_3^-$	24

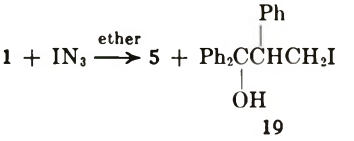
Somewhat similar results were obtained on INCO addition to 3,3-diphenylpropene (**10**) in ether. The resulting isocyanate was not isolated but converted with methanol to a crude carbamate. The latter was difficult to purify and was isolated in variable yield suggesting that it may consist of a mixture of isomers. However, only one pure carbamate product (**17**) could be isolated in 30–40% yield. Its structure was assigned on the basis of its mass spectrum (base peak at *m/e* 164, $PhCH{=}N^+HCO_2Me$) and zinc reduction to methyl *N*-(1,2-diphenyl-1-propyl)carbamate (**18**). The



structure of **18** was evident from its nmr and mass spectrum. The latter had the same characteristic base peak as **17**. The nmr spectrum indicated the presence of a *C*-methyl group as a doublet at τ 8.84 confirming the position of the iodo function in **17**.

In the BrN_3 addition to **10** in CH_3NO_2, the three-membered-ring bromonium ion is more easily equilibrated to a secondary carbonium ion than its analogous iodonium ion **15**;[9] hence, phenyl migration is more facile and only the rearranged product is observed.

The lack of formation of a 1,2 adduct of type **13** in the IN_3 addition to triphenylpropene **1** in acetonitrile is probably due to the higher propensity for phenyl migration in the trityl than in the diphenylmethyl system. When IN_3 was added to **1** in ether, **5** was obtained in 55% yield together with unreacted olefin and other products. Separation by chromatography led to the isolation of the iodohydrin **19** in 20% yield. This com-



pound was unstable and was converted upon standing in CCl_4 into 2,3-diphenylindene. The formation of the

(8) (a) F. W. Fowler, A. Hassner, and L. A. Levy, *J. Amer. Chem. Soc.*, **89**, 2077 (1967); (b) A. Hassner and F. W. Fowler, *J. Org. Chem.*, **32**, 2686 (1968).

(9) A. Hassner, F. Boerwinkle, and A. B. Levy, *J. Amer. Chem. Soc.*, **92**, 4879 (1970).

iodohydrin is probably due to the presence of water from incompletely dried AgN_3.

Experimental Section[10]

Ionic Addition of Bromine Azide to 3,3,3-Triphenylpropene (1).—Following the general procedure for BrN_3 additions in nitromethane,[9] 0.54 g (2 mmol) of triphenylpropene 1 was converted to 0.95 g of crude adduct. The product was placed in a quartz tube on 10 g of Woelm neutral alumina impregnated with 1% zinc silicate–manganese luminescent indicator. The column was eluted with CCl_4 (19 ml) until all the organic material was removed from the column, as judged by observation with a short-wave uv lamp. Removal of the solvent left 0.89 g (100%) of a partially solid product. Recrystallization from hexane gave two crops of crystals: 360 mg, mp 84–87°, and 179 mg, mp 84–92°. Another recrystallization of the first crop gave an analytical sample (prisms) of **7**: mp 86-88°; ir 2112 (N_3) and 633 cm^{-1} (CBr); nmr τ 2.5–3.1 (m, 13), 3.1–3.4 (m, 2), 5.8 (dd, 1, J = 2.2 and 11.2 Hz), 6.0 (dd, 1, J = 2.2 and 10.3 Hz), 6.42 (dd, 1, J = 11.2 and 10.3 Hz); mass spectrum m/e (rel intensity) 51 (10), 77 (43, Ph^+), 104 (20), 180 (100, Ph_2CN^+), 181 (16). A high resolution mass spectrum of **7** indicated that the ions at m/e 180 correspond to the elemental composition, $C_{13}H_{10}N$.

Anal. Calcd for $C_{21}H_{18}BrN_3$: C, 64.29; H, 4.63; N, 10.71. Found: C, 64.67; H, 4.74; N, 10.54.

Recrystallization of the second crop from hexane gave a mixture of **7** as pale yellow prisms, mp 84–87°, and of **3** as a white powdery solid, mp 120–125° (lit.[2] 125–127°). Using micro techniques, 3 mg of crystals of **3** were separated and analyzed: ir 631 cm^{-1} (CBr); uv (95% EtOH) λ_{max} 229 nm (ϵ 30,000), 276 (16,600).

Anal. Calcd for $C_{21}H_{17}Br$: C, 72.21; H, 4.91. Found: C, 72.77; H, 5.17.

Examination of the nmr spectra of the crude product showed, besides the peaks for the bromoazide **7**, a singlet at τ 5.71 (lit.[2] τ 5.59). An approximate integration of the peaks showed the original azide product to consist of 83% 3-azido-2,3,3-triphenylpropyl bromide (**7**), 7% 2,3,3-triphenylallyl bromide (**3**), and 11% 3,3,3-triphenylpropene (**1**).

Treatment of bromoazide **7** with potassium *tert*-butoxide in DMSO by the described procedure[3] afforded triphenylacrolein (**8**) in 55% yield.

Free-Radical Additions of Bromine Azide to 3,3,3-Triphenylpropene (1).—Following the described procedure,[4,9] 197 mg of **1** was stirred with a solution of BrN_3 in pentane (from 3.0 g of bromine) under N_2 for 27 hr in the presence of light and benzoyl peroxide. Work-up gave 248 mg of a solid consisting of 54% **1** and 30% **9**. Separation by preparative thick layer chromatography on silica gave pure adduct **9**: mp 96–100°; ir 2121 cm^{-1} (N_3); mass spectrum m/e (rel intensity) 51 (10), 77 (14), 115 (8), 165 (33), 178 (11), 180 (13), 243 [100, $(Ph_3)C^+$], 244 (19), 282 [3, $M\cdot^+ - (N_2 + H + HBr)$], 284 [9, $M\cdot^+ - (N_2 + Br)$], 363 (2, $M\cdot^+ - N_2$).

Anal. Calcd for $C_{21}H_{18}BrN_3$: C, 64.29; H, 4.63. Found: C, 64.39; H, 4.59.

Addition of Bromine to 3,3,3-Triphenylpropene (1).—Following the described procedure[2], 0.33 g (2.1 mmol) of bromine was added to 0.541 g (2 mmol) of **1** in CCl_4 to give after 48 hr a mixture of **2** and **3** in a ratio of 45:55 as determined by nmr integration.

When the same reaction was carried out in the dark in the presence of O_2 (bubbling O_2 into the CCl_4 for 5 min), the product contained 73% **3** and 11% **2**. In the presence of O_2 and a trace of di-*tert*-butylphenol, 0.886 g of product, mp 115–128°, was obtained which contained 88% **3** as indicated by the integration of the singlet at τ 5.72 *vs.* the aromatic multiplet. One crystallization from hexane–CCl_4 furnished pure allyl bromide **3**: mp 124–125° (lit.[2] 125–127°); mass spectrum m/e (rel intensity) 180 (100, $Ph_2C{=}N^+$).

3,3-Diphenylpropene (10).—Following the procedure of Corey, *et al.*,[11a] for preparation of 1,1-diphenylpropene, a solution of dimethyl sulfinyl anion in DMSO, prepared from 2.16 g (0.09 mol), of NaH and 55 ml of DMSO under N_2, was treated with 32.1 g (0.09 mol) of freshly prepared triphenylmethylphosphonium bromide[11b] in 90 ml of DMSO. After stirring for 25 min, a solution of 19.6 g (0.1 mol) of diphenylacetaldehyde in 30 ml of DMSO was added in one portion. This was stirred for 29 hr at 60°. The product was poured into 265 g of ice water and extracted with five 100-ml portions of Skellysolve B. The combined extracts were washed once with water, dried (Na_2SO_4), and evaporated to give 14.5 g (83%) of an oil. The nmr integration indicated a mixture of 65% 3,3-diphenylpropene, 10% 1,1-diphenylpropene, and 25% diphenylacetaldehyde. Other attempts using different proportions of NaH and $Ph_3P^+CH_3Br^-$ gave similar results. This mixture was taken up in 75 ml of ether and shaken with a solution of 25 g of $NaHSO_3$ in 75 ml of water for 5 min. After washing with three 75-ml portions of water, the product was dried ($MgSO_4$) and evaporated to give 11.9 g (68%) of an oil which was composed of 84% 3,3-diphenylpropene and 16% 1,1-diphenylpropene.

The mixture of isomers obtained above (11.9 g) was chromatographed on 400 g of 10% $AgNO_3$ on alumina. On elution with 1000 ml of hexane and solvent evaporation, 0.3 g of 1,1-diphenylpropene was obtained, mp 42–50° (lit.[11a] 48.5°), as indicated by an nmr doublet at τ 8.37. Elution with 300 ml of cyclohexane gave 1.4 g more of this isomer, mp 42–48°. Removal of 3,3-diphenylpropene from the column required 700 ml of benzene which gave, after rotary evaporation, 7.3 g of 3,3-diphenylpropene of *ca.* 95% isomeric purity. Further purification was easily accomplished by freezing the oil in a Dry Ice–acetone bath and adding 3 vol of pentane. The mixture was swirled in an ice bath until nearly dissolved and then placed in the freezer. Fractional crystallization over a period of 3–5 days gave pure 3,3-diphenylpropene, recovered by filtration through an ice-cooled Büchner funnel. This method of crystallization was applicable only to mixtures of over 90% isomeric purity. The product melted at 14.5–16° on a precooled stage and showed nmr and ir spectra matching those reported for **10**.[7,12]

Ionic Addition of Bromine Azide to 10.—The addition was carried out following the general procedure.[8] From 0.391 g (2.0 mmol) of 3,3-diphenylpropene (**10**) there was obtained 0.624 g (98%) of pale reddish oil, homogeneous by tlc. Both crude and chromatographed samples gave correct analysis. The adduct was inert to zinc–acetic acid, tertiary amines, and potassium *tert*-butoxide in ether suggesting the rearranged structure **11**: ir 2100 cm^{-1} (N_3); nmr (CCl_4) τ 2.8–3.2 (m, 10), 4.3–5.3 (m, 1), 6.1–7.0 (m, 3); mass spectrum m/e (rel intensity) 77 (15), 89 (16), 91 (66), 103 (15), 104 (100%, $PhCH{=}N^+$ and $Ph^+CHCH_2\cdot$), 115 (29), 165 (14), 169 (40), 171 (39), 178 (22), 179 (20), 180 (14), 183 (14), 185 (14), 273 (51, $M - HN_3$), 275 (50).

Anal. Calcd for $C_{15}H_{14}BrN_3$: C, 56.98; H, 4.46. Found: C, 57.14; H, 4.44.

Iodine Azide Addition to 3,3-Diphenylpropene (10) in Acetonitrile.—The addition[8] was carried out using 0.58 g (3 mmol) of **10**. The reaction mixtures were stirred for 19 hr and quenched to give on work-up 1.01 g (93%) of an oil which by nmr was shown to be 94% of adduct **13** and 6% of olefin **10**. Tlc using 2.5% ethyl acetate in hexane gave optimum separation into four fractions: R_f 0.18, 0.23, 0.34, and 0.50 (the last one was identical with diphenylpropene). A part of the product, 0.75 g, was subjected in three portions to preparative thick layer chromatography. Extraction with CH_2Cl_2 and rotary evaporation gave three fractions (total of 0.57 g), each showing strong azide absorption (*ca.* 2100 cm^{-1}) in the ir. The last fraction (3%) also had a strong peak at 1660 cm^{-1} suggesting a vinyl azide structure. The first fraction consisted of 80 mg (14%) of **3-azido-2,3-diphenyl-1-propyl iodide (12)** as an oil: mass spectrum m/e (rel intensity) 51 (13), 77 (57, Ph^+), 78 (16), 91 (19), 103 (17), 104 (100, $PhCH{=}N^+$), 105 (23), 165 (0), 167 (13).

Anal. Calcd for $C_{15}H_{14}IN_3$: C, 49.60; H, 3.89; I, 34.94. Found: C, 49.25; H, 3.93; I, 34.41.

The second fraction (0.47 g, 83%) consisted of **1-azido-3,3-**

(10) All solvents used were distilled. Melting points were determined on a Fisher block and are uncorrected. Infrared spectra were obtained using *ca.* 3% w/v solution in CCl_4 with a 0.5-mm KBr solution cell unless otherwise noted on a Perkin-Elmer 457 instrument. Nmr spectra were obtained on a Varian A-60 or A-60A spectrometer with TMS as an internal standard, using approximately a 20% w/v solution in $CDCl_3$. Uv spectra were recorded on a Cary 14 spectrometer. Mass spectra were obtained at 70 eV on a Varian MAT CH5 mass spectrograph. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Thin layer chromatographs were carried out on silica gel PF_{254} precoated plates or silica gel PF_{254} 2-mm coated plates for preparative layers.

(11) (a) R. Greenwald, M. Claykowsky, and E. J. Corey, *J. Amer. Chem. Soc.*, **78**, 1128 (1963); (b) G. Wittig and U. Schoellkopf, *Org. Syn.*, **40**, 66 (1960).

(12) C. L. Bumgardner, *J. Amer. Chem. Soc.*, **83**, 4423 (1961).

diphenyl-2-propyl iodide (13) which slowly solidified in the freezer, mp 47–60°. Chromatography of a small amount on 15 g of Woelm neutral alumina gave, on elution with benzene, a pure solid in the first fractions: 0.10 g; mp 56–58°; mass spectrum *m/e* (rel intensity) 51 (26), 77 (74), 78 (23), 91 (60), 103 (38), 104 (57), 105 (33), 115 (33), 117 (20), 130 (18), 152 (21), 165 (60), 166 (21), 167 (100, Ph_2CH^+), 178 (31), 179 (40), 180 (60), 181 (30), 193 (31), 208 (30).

Anal. Calcd for $C_{15}H_{14}IN_3$: C, 49.60; H, 3.88. Found: C, 49.86; H, 3.88.

3-Azido-1,1-diphenylpropene (14).—Elimination of HI from 0.18 g of 13 following the procedure of Hassner and Fowler[8] using 0.13 g of 1,5-diazobicyclo[4.3.0]-5-nonene (DBN) in acetone for 18 hr gave 0.127 g (100%) of 14 (82% pure by nmr integration). This was subjected to preparative thick layer chromatography using 2.5% ethyl acetate in hexane as an eluent to give 0.049 mg (42%) of the pure allylic azide 14 which solidified to give an analytical sample, mp 30–31°. Use of [2.2.2]-diazabicyclooctane in the same procedure gave a 53% yield of 14: ir 2112 (N_3) and 1599 cm^{-1} (C=C); nmr τ 2.4–2.9 (m, 10), 3.81 (t, 1, J = 7.5 Hz), 6.16 (d, 2, J = 7.5 Hz); uv (95% EtOH) λ_{max} 230 nm (ϵ 14,500), 253 (14,500).

Anal. Calcd for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.34; H, 5.42; N, 17.65.

General Procedure for Iodine Azide Addition in Ether.—A predried 50-ml three-necked flask fitted with a mechanical stirrer and gas outlet was connected directly to an apparatus for distilling ether from $LiAlH_4$. The flask and distillation apparatus were flushed with a stream of dry nitrogen and *ca.* 10 ml of ether was distilled into the flask. Silver azide was freshly prepared by mixing 0.68 g (4.04 mmol) of $AgNO_3$ in 20 ml of distilled water and 0.260 g (4.00 mmol) of NaN_3 in 4 ml of distilled water in an ice bath. The azide was filtered through a coarse sintered glass funnel fitted with a piece of glass fiber filter paper and was quickly washed with three 10-ml portions of distilled water and five 10-ml portions of anhydrous ether. The cake of AgN_3 was transferred immediately into the reaction flask using a Nalgene powder funnel. (*Caution!* Dry silver azide is extremely shock sensitive.) The flask was covered with a serum stopper and connected with a reflux condenser–drying tube. The mixture was cooled to −80° in a Dry Ice–acetone bath and stirred during the rapid addition of 0.488 g (3 mmol) of ICl. The flask was covered with foil and an ice bath was substituted for cooling. The solution was stirred an additional 10–15 min, 2 mmol of the olefin was added, and the ice bath was removed. After being stirred for 15–24 hr more, the reaction mixture was forced through Celite 545 into a saturated $NaHSO_3$ solution. The same work-up was used as described for IN_3 additions in acetonitrile.[8] Deviations are noted for specific compounds.

Addition of IN_3 to 3,3-Diphenylpropene (10) in Ether.—Using the general procedure, 0.433 g (2.03 mmol) of 3,3-diphenylpropene (10) was converted into 0.624 g (88%) of adduct. Nmr spectra showed that *ca.* 20% of the starting olefin was left unreacted. Elution of 0.48 g of the product in two portions gave 0.42 g of recovered product consisting of five fractions. The first fraction 72 mg (17%) was identified as 3,3-diphenylpropene (10) by ir. Recovery of the next two fractions gave 133 mg of 12 (32%) and 137 mg of 13 (33%). Ir and mass spectra for these compounds were identical with those given above. The fourth fraction, 12 mg (3%), appeared to be a vinyl azide (ir 2100 and 1660 cm^{-1}) and the fifth, 69 mg (15%), gave only a weak azide peak in the ir. Further indentification of these compounds was not attempted.

Addition of IN_3 to 3,3,3-Triphenylpropene (1) in Ether.—From 0.54 g (2.00 mmol) of 3,3,3-triphenylpropene (1) was obtained 0.859 g (98%) of an oil. Elution of two 0.24-g portions of the product on preparative layer chromatograms using 5% ethyl acetate in hexane gave five fractions (0.37-g total). Unreacted 1 (24 mg, 7% of recovered material) was found to be in the first fraction. The ir of the second (60 mg, 16%) and fourth (8 mg, 2%) fractions failed to show azide absorptions and further identification was not attempted. The third fraction (205 mg, 55%) proved to be 3-azido-2,3,3-triphenyl-1-propyl iodide (5) by comparison of ir and nmr spectra.

The fifth fraction gave 71 mg (20%) of a brown-white solid: mp 120–125° dec; nmr (CCl_4) τ 2.4–3.2 (m, 15), 5.83 (2 d, 1), 6.43 (m, 2), 7.5 (s, 1). Cooling of the nmr sample in CCl_4 after *ca.* 2 hr at 25° gave 19 as a white crystalline solid, mp 99–101° dec.

Anal. Calcd for $C_{21}H_{19}IO$: C, 60.88; H, 4.62. Found: C, 60.62; H, 4.54.

When a solution of 19 in CCl_4 was allowed to stand for 24 hr, evaporation yielded crude 2,3-diphenylindene, mp 100–105° (lit. 110–112°), identified by ir and nmr comparison with an authentic sample.[2,3]

Methyl *N*-(3-Iodo-1,2-diphenyl-1-propyl)carbamate (17).—Addition of iodine isocyanate[13] to diphenylpropene 10 and treatment with methanol gave the crude 1,3-iodo carbamate 17 in variable yields (55–80%). Recrystallization from methanol gave an analytical sample: mp 167–169°; white needles; ir 3450 (NH), 1710 cm^{-1} (C=O); nmr τ 2.7–3.2 (m, 10), 4.7–5.2 (m, 2), 6.43 (s, 3), 6.5–7.0 (m, 2); mass spectrum *m/e* (rel intensity) 42 (19), 43 (12), 57 (13), 77 (14), 78 (10), 104 (33), 121 (11), 132 (10), 149 (13), 164 (100, $PhCH{=}N^+HCO_2CH_3$), 165 (12).

Anal. Calcd for $C_{17}H_{18}INO_2$: C, 51.62; H, 4.59; N, 3.54. Found: C, 51.29; H, 4.41; N, 3.54.

Methyl *N*-(1,2-Diphenyl-1-propyl)carbamate (18).—Reduction of 17 (0.190 g, 0.48 mmol) in 0.75 ml of acetic acid was carried out with 0.1 g of freshly activated zinc[14] at 70°. After stirring magnetically for 2 hr at 70°, the mixture was filtered, neutralized with solid Na_2CO_3, and extracted with ether. Evaporation gave a white powdery solid, mp 120–133°, yield 0.139 g (100%). Recrystallization from methanol gave 49 mg (38%) of an analytical sample: mp 142–143°; nmr τ 2.75 (s, 10), 4.9–5.4 (m, 1), 6.50 (s, 3), 6.99 (p, 1), 8.84 (d, 3); mass spectrum *m/e* (rel intensity) 42 (35), 59 (10), 77 (12), 104 (10), 105 (12), 121 (16), 164 (100, $PhCH{=}N^+HCO_2CH_3$).

Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11. Found: C, 75.99; H, 6.98.

Registry No.—**1**, 3282-07-3; **3**, 16536-01-9; **7**, 29182-53-4; **9**, 29182-54-5; **10**, 3542-14-1; **11**, 29182-56-7; **12**, 29182-57-8; **13**, 29182-58-9; **14**, 29182-59-0; **17**, 29182-60-3; **18**, 29182-61-4; **19**, 29182-62-5; bromine azide, 13973-87-0; iodine azide, 14696-82-3.

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Notes

Synthesis of 5-Oxohexenoic Acid[1a]

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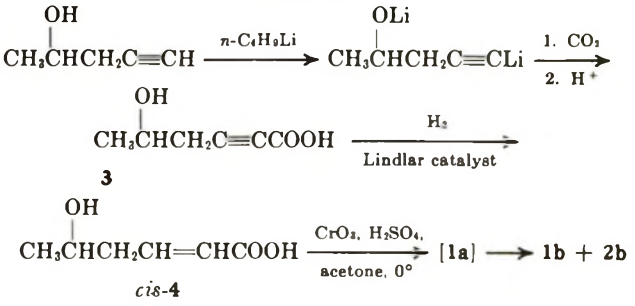
Poly-β-keto acids are postulated as intermediates in the biosynthesis of many phenolic natural products.[2] Certain of these aromatic compounds lack one or more of the hydroxyl groups that would be expected to result from cyclization of simple poly-β-keto acids. Birch has suggested that reduction of one or more keto groups occurs prior to cyclization. Support for this proposal has been obtained recently by Lynen and coworkers from studies of the biosynthesis of 6-methylsalicylic acid by a purified enzyme complex of *Penicillium patulum*.[3] These results suggest that reduction and dehydration of enzyme-bound 3,5-dioxohexanoic acid occur to give 5-oxohexenoate, condensation of which with malonyl coenzyme A to give 3,7-dioxo-4- (or 5-) octenoic acid followed by cyclization affords 6-methylsalicylic acid. The double bond must have the cis configuration in order for cyclization to occur.

The possible biological role of 5-oxohexenoic acid (**1a** or **2a**) prompted us to undertake a synthesis of it which could be adapted readily to isotopic incorporation; the paucity of information available on the synthesis and properties of simple 5-oxoalkenoic acids provided a further stimulus for this investigation.[4-9]

$CH_3COCH_2CH{=}CHCOOH$	$CH_3COCH{=}CHCH_2COOH$
1a (cis)	**2a** (cis)
b (trans)	**b** (trans)

The present synthesis (Scheme I) aimed toward the synthesis of *cis*-5-oxo-2-hexenoic acid (**1a**) was designed to permit efficient introduction of the ^{14}C label at the 1 position. Commercially available 4-pentyn-2-ol was converted to its dilithium salt by reaction with *n*-butyllithium. Treatment of this salt with a large excess of Dry Ice gave a 41% yield of 5-hydroxy-2-hexynoic acid (**3**) after chromatography. The reaction is a variation of one by Haynes and Jones which employed carbon dioxide under pressure for carboxylation of the magnesium salt of 4-pentyn-2-ol.[10]

SCHEME I



Acetylenic acid **3** was selectively reduced to cis olefinic acid **4** by hydrogenation with Lindlar catalyst. Cyclization of **4** to give 5,6-dihydro-6-methyl-2-pyrone[10,11] occurs readily; consequently purification of **4** was not attempted and oxidation of the hydroxyl group was carried out immediately.

The oxidation was performed with Jones reagent in acetone at 0°. Work-up of the reaction followed by chromatography gave 5-oxohexenoic acid as a pale yellow oil in 16% yield based on **3**. The structure of the keto acid was supported by the mass spectrometric molecular weight determination and by elemental analyses.

The nmr spectrum of freshly prepared material indicated that the intended product **1a** had undergone isomerization to give a mixture of the trans isomers **1b** and **2b**, with **1b** predominating. Neither the cis isomers **1a** and **2a** nor any enol structures could be detected. Evidence for the enolization–ketonization process was obtained by equilibration of a chloroform solution of the keto acid mixture with deuterium oxide; exchange of the C-2 and C-4 protons of both **1b** and **2b** occurred with a half-life of approximately 5 hr.

The uv spectrum of the mixture of keto acids in ethanol consisted of an intense band at 214 nm (ε 10,500) and a weaker broad band centered at 290 nm (ε 905). The short wavelength maximum presumably is an unresolved composite of **1b** and **2b**. The maximum of the former would be expected near 205 nm and that of the latter would be near 220 nm.[12] The long wavelength band is too intense to arise solely from $n \rightarrow \pi^*$ excitation of the carbonyl groups and is possibly the contribution of a small quantity of one or more of the enolized forms of **1b** and **2b**.

Treatment of the mixture of keto acids with 2,4-dinitrophenylhydrazine gave a single hydrazone. The ir and uv spectra indicated that it was the trans Δ^3 isomer.[14]

No further attempts were made to prepare and isolate

(1) (a) This investigation was supported by the General Medical Sciences Institute of the National Institutes of Health, U. S. Public Health Service, Grant No. GM-12848, and by the Alfred P. Sloan Foundation. (b) Research Career Development Awardee, K3-GM-27013, of the National Institutes of Health, U. S. Public Health Service.

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(11) See U. Eisner, J. A. Elvidge, and R. P. Linstead, *ibid.*, 1372 (1953).

(12) Compare with crotonic acid [204 nm (ε 11,500)[8]] and *trans*-3-penten-2-one [220 nm (ε 13,300) and 310 (ε 41)[13]].

(13) R. Heilmann, G. de Gaudemaris, and P. Arnaud, *Bull. Soc. Chim. Fr.*, **24** (5), 119 (1957).

(14) See H. O. House and R. S. Ro, *J. Amer. Chem. Soc.*, **80**, 2428 (1958).

a single cis isomer of 5-oxohexenoic acid. In view of the facile tautomerism of these acids, it appears that under the conditions of most metabolic experiments a mixture of isomers would rapidly be formed.

The synthesis of 1-^{14}C-labeled 5-oxohexenoic acids **1b** and **2b** was carried out using a stoichiometric amount (*i.e.*, equal to the amount of butyllithium) of carbon dioxide generated from ^{14}C-labeled barium carbonate. The yield of **3** was comparable with that obtained previously with a large excess of carbon dioxide. The reduction of **3** and subsequent oxidation were carried out in a manner identical with the previous synthesis of unlabeled material.

Experimental Section[15]

Preparation of 5-Hydroxy-2-hexynoic Acid (3).—A hexane solution of *n*-butyllithium (45 ml containing 0.11 mol) was added cautiously to a stirred solution of 3.36 g (0.040 mol) of 4-pentyn-2-ol (K & K Laboratories) in 100 ml of anhydrous ether at 0° under nitrogen. The white suspension was stirred for 3 hr at room temperature and then poured over crushed Dry Ice. The product was isolated by addition of 10 ml of cold 6 *M* hydrochloric acid and thorough extraction into ether. The ethereal solution was dried ($MgSO_4$) and evaporated to leave 3.6 g of oil which was chromatographed on 15 g of silica gel. Elution was carried out with ether–hexane (1:4) and ether. The latter fraction contained 2.12 g (41%) of **3**: mp 52–54° (lit.[10] mp 58°); nmr ($CDCl_3$) 1.31 (3, d, J = 6.5 Hz, CH_3), 2.56 (2, d, J = 5.5 Hz, CH_2), 4.13 (1, t × q, J = 6.5 and 5.5 Hz, respectively, CH), and 7.6 (2, broad singlet, OH and CO_2H); ir (molten) 3400 (broad), 2240, 1700 cm^{-1}. No impurities were detectable by nmr or tlc; the material was used without further purification.

Preparation of *cis*-5-Hydroxy-2-hexenoic Acid (4).—Lindlar catalyst[16] (250 mg) was suspended in 40 ml of freshly distilled tetrahydrofuran in a 250-ml flask attached to a Brown hydrogenator arranged for external hydrogenation.[17] After the system had been flushed with hydrogen, 0.578 g (4.5 mmol) of **3** in 2 ml of tetrahydrofuran was introduced by a syringe. Reduction was stopped after rapid hydrogen uptake ceased (*ca.* 20 min). The catalyst was filtered off and the solvent was removed *in vacuo* to give reasonably pure **4** as a pale yellow oil in essentially quantitative yield: nmr ($CDCl_3$) 1.25 (3, d, J = 6 Hz, CH_3), 2.83 (2, t × d, J = 7 and 2 Hz, respectively, CH_2), 3.92 (1, m, 5 CH), 5.93 (1, d × d, J = 12 and 2 Hz, 2 CH), 6.45 (1, d × t, J = 12 and 7 Hz, respectively, 3 CH), and 7.86 (2, broad s, OH and COOH); ir (neat) 3300 (broad), 2550, 1690, 1645, 1420, 1375 cm^{-1}.

Preparation of 5-Oxohexenoic Acids 1b and 2b.—Hydroxy acid **4** obtained in the above reaction was dissolved immediately in 5 ml of reagent grade acetone and cooled to 0°; 1.2 ml of Jones reagent[18] was added dropwise. After the addition was complete, the reaction was stirred for 10 min and poured into ice water. The solution was extracted continuously with ether. The ether extract was dried ($MgSO_4$) and evaporated to leave 0.476 g of crude keto acids. The material was chromatographed on 15 g of silica gel which had been treated with 0.3 ml of 0.5 *N* sulfuric acid. The column was eluted with chloroform, chloroform–ether mixtures, and then ether. The fraction eluted with ether gave 0.091 g (16% based on **3**) of a pale yellow oil which was a mixture of **1b** and **2b**. An analytical sample was prepared by rechromatography: nmr ($CDCl_3$) (for **1b**) 2.23 (3, s, CH_3), 3.42 (2, d × d, J = 7 and 1.5 Hz, CH_2), 5.90 (1, d × t, J = 15 and 1.5 Hz, respectively, 2 CH), 6.93 (1, d × t, J = 15 and 7 Hz, respectively, 3 CH), and 12.7 (1, broad s, OH); nmr (for **2b**) 2.32 (3, s, CH_3), 3.33 (s, d × d, J = 7 and 1.5 Hz, CH_2), 6.18 (1, d × t, J = 16.5 and 1.5 Hz, respectively, 4 CH), 6.93 (1, d × t, J = 16.5 and 7 Hz, respectively, 3 CH), 12.7 (1, broad s, OH); ir (neat) 2650, 1710, 1680, 1640, 1420, 1360, 1270, 1160, and 980 cm^{-1}; uv 290 nm (broad, ϵ 905) and 214 (ϵ 10,500); mass spectrum[19] *m/e* 58 (17), 68 (100), 71 (52), 81 (17), 84 (42), 85 (23), 95 (10), 110 (25), 113 (48), and 128 (7).

Anal. Calcd for $C_6H_8O_3$: C, 56.25; H, 6.29. Found: C, 55.97; H, 6.49.

After a similar preparation of 5-oxohexenoic acid, the crude product, prior to chromatography, was converted to the 2,4-dinitrophenylhydrazone derivative, mp 157–160°. Chromatography on silica gel with elution by ethyl acetate gave orange needles of the derivative of **2b**: mp 177.5–178°; nmr (acetone-d_6 and DMSO-d_6) 2.23 (3, s, CH_3), 3.28 (2, m, CH_2), 4.75 (2, broad 2, OH and NH), 6.45 (2, m, CH=CH), 7.95 (1, d, J = 9 Hz, aromatic 6 H), 8.41 (1, d × d, J = 9 Hz, aromatic 5 H), 8.95 (1, d, J = 2 Hz, aromatic 3 H); ir (KBr) 1710, 1620, and 1595 cm^{-1}; uv 372 nm (ϵ 22,600).[14]

Anal. Calcd for $C_{12}H_{12}N_4O_6$: C, 46.76; H, 3.92; N, 18.18. Found: C, 46.79; H, 3.90; N, 18.00.

The derivative of **1b** was not detected.

Preparation of 1-^{14}C-5-Oxohexenoic Acid.—A vacuum manifold was used for this procedure. The reaction vessel was a magnetically stirred 250-ml round-bottomed flask with a side arm equipped with a serum cap. The flask was flushed with nitrogen, evacuated, and closed off. A solution of 4-pentyn-2-ol (1.0 g, 12.0 mmol) in 50 ml of ether was introduced by a syringe. The vessel was cooled with an ice–acetone bath and 23.8 mmol of *n*-butyllithium in hexane was introduced. The reaction flask was opened briefly to the pump to remove butane which had been generated. The mixture was allowed to stand at room temperature for 18 hr. The carbon dioxide generating system consisted of a 50-ml stirred flask containing 4.70 g of ^{14}C-labeled barium carbonate (23.8 mmol, *ca.* 0.3 mc) and equipped with an addition funnel containing 20 ml of concentrated sulfuric acid. A drying tube containing Drierite separated the generating system from the manifold. The generating system was evacuated, the reaction vessel was cooled with a Dry Ice–acetone bath, and then the two systems were opened to each other. Sulfuric acid was added slowly. After the reaction was complete, the reaction vessel was cooled in a liquid nitrogen bath to ensure complete transfer of carbon dioxide. The reaction vessel was then isolated and allowed to warm to room temperature. After 3 hr the reaction flask was removed from the manifold and its contents were poured into a mixture of 5 ml of sulfuric acid and 50 g of ice. The solution was extracted three times with ether; the ethereal solutions were combined, dried, and evaporated to leave 1.30 g of crude product which was chromatographed as described above to yield 0.674 g (44%) of **3**, mp 56–58°, specific activity 5.27 × 10^6 dpm/mmol. The material was carried through the reduction and oxidation steps described above to give, after chromatography, 350 mg of a mixture of **1b** and **2b**. Rechromatography of a center fraction gave 30 mg of material having a specific activity of 5.35 × 10^6 dpm/mmol. The radiochemical purity was demonstrated by counting increments of a thin layer chromatogram.

Registry No.—**1b**, 28845-67-2; **2b**, 28845-68-3; **2b** 2,4-DNP, 28845-69-4; **3**, 16427-77-3; **4**, 28845-71-8.

(15) Ir and uv spectra were obtained with Beckman IR-10 and DB spectrometers, respectively. Uv spectra were determined with solutions in 95% ethanol. Nmr spectra were determined with a Varian A-60 spectrometer employing tetramethylsilane as the internal standard. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

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

(17) R. L. Augustine, "Catalytic Hydrogenation, Techniques and Applications in Organic Syntheses," Marcel Decker, New York, N. Y., 1965, pp 15–20.

(18) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2555 (1953).

(19) The mass spectrum was obtained with an LKB-9000 mass spectrometer by Mr. Charles Wetter. The sample was introduced with the direct insertion probe; the ionizing energy was 70 eV.

Return-Rearrangement in Solvolyses. Triangular Kinetic Schemes

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One of the most extensively studied classes of reactions in modern physical organic chemistry has been the solvolyses of sulfonate esters. The rates of such

solvolyses are commonly measured by titrimetrically monitoring liberated sulfonic acid or lyate ion depletion. The derived rate constant k_t (eq 1) is assumed to reflect $k_{ionization}$ when an SN1 mechanism is operative.

$$\text{ROTs} \xrightarrow[\text{SOH}]{k_t} \text{ROS} + \text{HOTs}$$

$$-\frac{d[\text{ROTs}]}{dt} = \frac{d[\text{HOTs}]}{dt} = k_t[\text{ROTs}]$$

$$\ln\left(\frac{[\text{HOTs}]_\infty - [\text{HOTs}]_0}{[\text{HOTs}]_\infty - [\text{HOTs}]_t}\right) \equiv k_t t \qquad (1)$$

The situation can become considerably more complex if rearrangement of the starting material to an isomeric sulfonate is concurrent with acid production (eq 2). This situation is not at all uncommon.[1-5]

$$\begin{array}{ccc} \text{ROTs} & \xrightarrow{k_1} & \\ \downarrow{\scriptstyle k_2} & & \text{HOTs} + \text{products} \\ \text{R'OTs} & \xrightarrow{k_3} & \end{array} \qquad (2)$$

In cases[6] where $k_3 \ll k_1$ the kinetic situation is simply that of two parallel reactions, with the specific rate of disappearance of ROTs ($k_t = k_1 + k_2$) directly calculable by use of eq 1 and the experimental infinity titer, which will be $k_1/(k_1 + k_2)$ times the theoretical infinity titer.[7]

The situation becomes even more complex if $k_1 \approx k_3$[1-5] since the rearranged sulfonate contributes significantly to the liberated acid, exaggerating the experimental infinity titer. In such instances first-order plots become decidedly nonlinear. One approach to the problem when $k_3 < k_1$ is to simulate values of the infinity titer until a plot of ln ($[\text{HOTs}]_\infty - [\text{HOTs}]_t$) *vs.* time becomes linear (or nearly so), thus yielding adjusted values of $k_1 + k_2$.[5-8] It was recently stated[5] that this simulation technique is equivalent to the equation

$$[\text{HOTs}]_t = [\text{ROTs}]_0\left(1 - \frac{k_2 e^{-k_3 t}}{k_1 + k_2 - k_3} - \frac{(k_1 - k_3)e^{-(k_1+k_2)t}}{k_1 + k_2 + k_3}\right) \qquad (3)$$

That this equation is incorrect can be most easily seen by setting $k_3 = 0$, in which case eq 3 should[7] reduce to

$$[\text{HOTs}]_t = \frac{[\text{ROTs}]_0 k_1}{k_1 + k_2}(1 - e^{-(k_1+k_2)t}) \qquad (4)$$

which it does not.

If one treats eq 2, carefully avoiding the steady-state approximation for R'OTs, the following equations are generated.[9]

$$[\text{ROTs}]_t = [\text{ROTs}]_0 e^{-(k_1+k_2)t}$$

$$\frac{d[\text{R'OTs}]}{dt} = k_2[\text{ROTs}]_0 e^{-(k_1+k_2)t} - k_3[\text{R'OTs}]_t \qquad (5)$$

Equation 5 is an inexact differential equation which can be solved by use of the integrating factor $\exp(k_3 t)$ to give

$$[\text{R'OTs}]_t = \frac{k_2[\text{ROTs}]_0}{k_1 + k_2 - k_3}(e^{-k_3 t} - e^{-(k_1+k_2)t}) \qquad (6)$$

With the mass-balance relationship

$$[\text{HOTs}]_t = [\text{ROTs}]_0 - [\text{ROTs}]_t - [\text{R'OTs}]_t \qquad (7)$$

eq 6 yields

$$[\text{HOTs}]_t = [\text{ROTs}]_0\left[1 - e^{-(k_1+k_2)t} - \frac{k_2}{k_1 + k_2 - k_3}\left(e^{-k_3 t} - e^{-(k_1+k_2)t}\right)\right] =$$

$$[\text{ROTs}]_0\left[1 + \frac{(k_3 - k_1)e^{-(k_1+k_2)t} - k_2 e^{-k_3 t}}{k_1 + k_2 - k_3}\right] \qquad (8)$$

Although not too different in form from eq 3, eq 8 readily reduces to eq 4 when $k_3 = 0$.[10] Other situations in which eq 8 reduces to more familiar forms are (a) $k_3 \gg k_1 \approx k_2$

$$[\text{HOTs}]_t = [\text{ROTs}]_0(1 - e^{-(k_1+k_2)t}) \qquad (8a)$$

as would be expected for two parallel acid-producing pathways, and (b) $k_2 \gg k_1$ and $k_2 \neq k_3$[9]

$$[\text{HOTs}]_t = [\text{ROTs}]_0\left[1 + \left(\frac{k_3 e^{-k_3 t} - k_2 e^{-k_2 t}}{k_2 - k_3}\right)\right] \qquad (8b)$$

for two consecutive first-order pathways. Notice also that (c) if $k_1 = k_3$

$$[\text{HOTs}]_t = [\text{ROTs}]_0(1 - e^{-k_1 t}) \qquad (8c)$$

and thus even if $k_2 \gg k_1$, the contribution of rearrangement to k_t will escape detection.[11]

At this point another question might arise. Does the scheme in eq 2 adequately represent the "true" mechanism shown in eq 9? By applying the steady-state

$$\begin{array}{ccccc} \text{ROTs} & \xrightarrow{k_i} & |\text{ion pair}| & \xrightarrow{k_s} & \text{HOTs} + \text{products} \\ & & {\scriptstyle k_r}\downarrow\uparrow{\scriptstyle k_i'} & & \\ & & \text{R'OTs} & & \end{array} \qquad (9)$$

approximation to the ion-pair intermediate it is found that

$$\frac{d[\text{R'OTs}]}{dt} = k_r[\text{ion pair}]_t - k_i'[\text{R'OTs}]_t =$$

$$K_1 e^{-k_i t} - K_2[\text{R'OTs}]_t \qquad (10)$$

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(1) T. L. Jacobs and R. S. Macomber, *J. Amer. Chem. Soc.*, **91**, 4824 (1969).

(2) R. S. Macomber, *ibid.*, **92**, 7101 (1970).

(3) W. G. Young, S. Winstein, and H. L. Goering, *ibid.*, **73**, 1958 (1951).

(4) S. Winstein and K. C. Schreiber, *ibid.*, **74**, 2171 (1952).

(5) L. A. Paquette and P. C. Storm, *ibid.*, **92**, 4295 (1970). We wish to thank Provessor Paquette for a listing of his program.

(6) E. L. Allred and S. Winstein, *ibid.*, **89**, 4012 (1967).

(7) It is important to realize that for parallel reactions, such as eq 2 with $k_3 = 0$ and starting exclusively with ROTs

$$[\text{ROTs}]_t = [\text{ROTs}]_0 e^{-(k_1+k_2)t}$$

$$[\text{HOTs}]_t = \frac{[\text{ROTs}]_0 k_2}{k_1 + k_2}(1 - e^{-(k_1+k_2)t})$$

$$[\text{R'OTs}]_t = \frac{[\text{ROTs}]_0 k_2}{k_1 + k_2}(1 - e^{-(k_1+k_2)t})$$

and more important

$$\frac{d}{dt}\ln[\text{ROTs}] = \frac{d}{dt}\ln([\text{R'OTs}]_\infty - [\text{R'OTs}]_t) =$$

$$\frac{d}{dt}\ln([\text{HOTs}]_\infty - [\text{HOTs}]_t) = -(k_1 + k_2)$$

K. L. Servis and J. D. Roberts, *Tetrahedron Lett.*, 1369 (1967).

(8) A better approach[3,4] involves calculation of "instantaneous" rate constants which lead to "true" values of $[\text{ROTs}]_t$. In our hands this method yielded values of k_{1-3} about 0.5–1.5 times greater than the values obtained from the simulation treatment.[5] Another advantage of the former technique is that it is equally applicable when $k_3 > k_1$. For a related approach see S. J. Cristol and D. D. Tanner, *J. Amer. Chem. Soc.*, **86**, 3122 (1964).

(9) Equation 6 is the general solution of eq 5, but requires that $k_1 + k_2 \neq k_3$. If coincidentally $k_1 + k_2 = k_3$, the solution of eq 5 is

$$[\text{R'OTs}]_t = [\text{ROTs}]_0 k_2 t e^{-k_3 t}$$

$$[\text{HOTs}]_t = [\text{ROTs}]_0[1 - (k_3 t + 1)e^{-k_3 t}]$$

(10) It is to be expected that the computer simulation technique will yield satisfactory results only when $k_3 << k_1$.

(11) This would be the situation with such systems as 2-norbornyl and 3-phenyl-2-butyl.

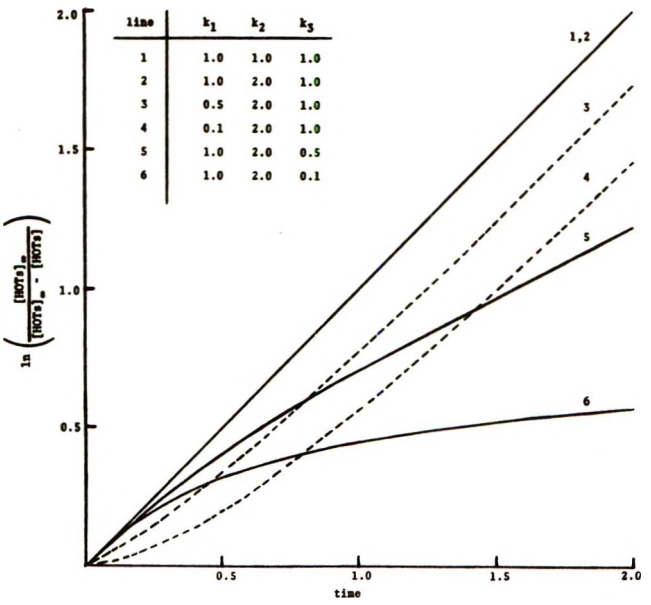

Figure 1.—Plots of $\ln\{[HOTs]_\infty/([HOTs]_\infty - [HOTs]_t)\}$ *vs.* time for various values of k_1, k_2, and k_3 (eq 8).

where $K_1 = k_i k_r[ROTs]_0/(k_s + k_r)$ and $K_2 = k_i' k_s/(k_s + k_r)$. Solution of eq 10 as for eq 5 leads to

$$[R'OTs]_t = \frac{k_i k_r[ROTs]_0}{k_i' k_s - k_i k_s - k_i k_r}\left[e^{-k_i t} - e^{-\left(\frac{k_i' k_s}{k_s + k_r}\right)t}\right] \quad (11)$$

Applying the mass-balance relationship (eq 7), eq 11 gives

$$[HOTs]_t = [ROTs]_0\left[1 - \frac{k_s(k_i - k_i')e^{-k_i t} + k_i k_r e^{-\left(\frac{k_i' k_s}{k_s + k_r}\right)t}}{k_i k_s + k_i k_r - k_i' k_s}\right] \quad (12)$$

One may consider the following special cases of eq 12.

(a) $k_r = 0$:

$$[R'OTs]_t = 0 \text{ and } [HOTs]_t = [ROTs]_0(1 - e^{-k_i t}) \quad (12a)$$

(b) $k_i' = 0$:

$$[HOTs]_t = \frac{k_s[ROTs]_0}{k_s + k_r}(1 - e^{-k_i t}) \quad (12b)$$

(c) $k_i = k_i'$:

$$[HOTs]_t = [ROTs]_0\left[1 - e^{-\left(\frac{k_i' k_s}{k_s + k_r}\right)t}\right] \quad (12c)$$

In both eq 12a and 12b it can be seen that k_t (eq 1) is to be identified with k_i, while in the case of eq 12c k_t will equal k_i $(= k_i')$ only if $k_r \ll k_s$, but above all it can be seen that

$$k_1 = \frac{k_i k_s}{k_s + k_r} \qquad k_2 = \frac{k_i k_r}{k_s + k_r} \qquad k_3 = \frac{k_i' k_s}{k_s + k_r}$$

and if $k_i \gg k_i'$

$$k_t = k_1 + k_2 = \frac{k_i k_s + k_i k_r}{k_s + k_r} = k_i$$

Thus the mechanism shown in eq 2 *is* an adequate representation of the "true" mechanism given in eq 9.

It is usually stated[1-5] that negative curvature in first-order plots of eq 1 indicates that $k_1 > k_3$ (or $k_i > k_i'$) and that positive curvature implies the converse. From eq 8 we see[9]

$$\frac{d}{dt}\ln\left(\frac{[HOTs]_\infty}{[HOTs]_\infty - [HOTs]_t}\right) = \frac{d}{dt}\ln\left[\frac{k_1 + k_2 - k_3}{k_2 e^{-k_3 t} + (k_1 - k_3)e^{-(k_1 + k_2)t}}\right] \quad (13)$$

Negative curvature will appear only if $k_3 < k_1$ *and* $k_1 \lesssim k_2$. Similarly positive curvature requires that $k_3 > k_1$ *and* $k_2 \gtrsim k_1$. Thus for there to be any deviation from linearity k_2 must be at least comparable in magnitude to k_1. Sample plots with various relative values of k_1, k_2, and k_3 are shown in Figure 1.[12] As may be obvious from eq 13, lines 3 and 4 (positive curvature) as well as lines 5 and 6 (negative curvature) all approach having slopes equal to k_3 as $t \to \infty$.

Acknowledgments.—We wish to thank Professor Paul von R. Schleyer for a stimulating discussion. Acknowledgment is made to the donors of the Petroleum Research Fund of the American Chemical Society for support of this work.

(12) A FORTRAN IV program has been written which permits best values for k_1, k_2, and k_3 (eq 2) to be calculated. The program is of the interactive on-line variety, making use of a remote console. Initial estimates of the rate constants are progressively refined until the deviation between calculated and experimental values of $\ln\{[HOTs]_\infty/([HOTs]_\infty - [HOTs]_t)\}$ reaches an acceptable value. A listing of the program will be supplied upon request.

Synthesis of Mandelaldehyde Dimers

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As a model system for gaining information concerning the interconversion between glyceraldehyde and dihydroxyacetone, the isomerization of mandelaldehyde to 2-hydroxyacetophenone has been studied.[2] For this purpose it was necessary to secure mandelaldehyde itself, 1-deuteriomandelaldehyde, and several para-substituted mandelaldehydes; this paper describes the syntheses of these substances.

In an early attempt to prepare mandelaldehyde (**5a**) by the acid-catalyzed hydrolysis of mandelaldehyde acetate, Nef obtained only 2-hydroxyacetophenone as the product.[3] More recently, successful syntheses have been effected by oxidative hydrolysis of the dimethyl thioacetal by means of bromine[4] and iodine,[5] the product in both cases being identified on the basis of the infrared spectrum as the dimer of mandelaldehyde (**6a**). In the present scheme, simple acid-catalyzed hydrolysis of mandelaldehyde dimethyl acetal proved to be effective. The dimethyl acetal **4a** was synthesized by lithium aluminum hydride reduction of the dimethyl acetal of phenylglyoxal **3a** which, in turn, was prepared by the action of trimethyl orthoformate and methanol on phenylglyoxal **2a**.

The amorphous white powder obtained from the hydrolysis of **4a** had an elemental analysis compatible with a $(C_8H_8O_2)_n$ compound, showed a strong ir band at 1140 cm^{-1} characteristic of a C–O–C linkage, and was trans-

(1) National Aeronautics and Space Administration Predoctoral Trainee, 1966–1969; National Science Foundation Predoctoral Trainee, 1969–1970.
(2) D. W. Griffiths and C. D. Gutsche, *J. Amer. Chem. Soc.*, in press.
(3) J. U. Nef, *Justus Liebigs Ann. Chem.*, **335**, 247 (1904).
(4) F. Weygand, H. J. Bestmann, H. Ziemann, and E. Klieger, *Chem. Ber.*, **91**, 1043 (1958).
(5) G. A. Russell and L. A. Ochrymowycz, *J. Org. Chem.*, **34**, 3618 (1969).

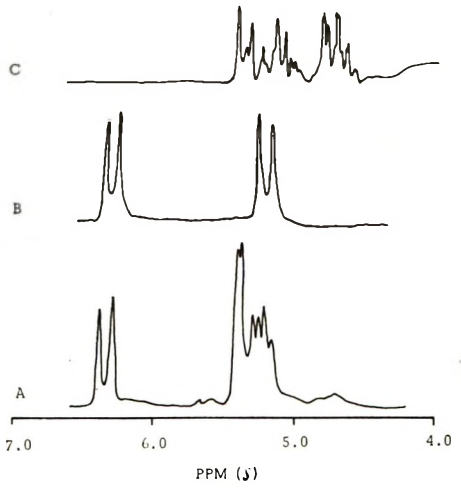
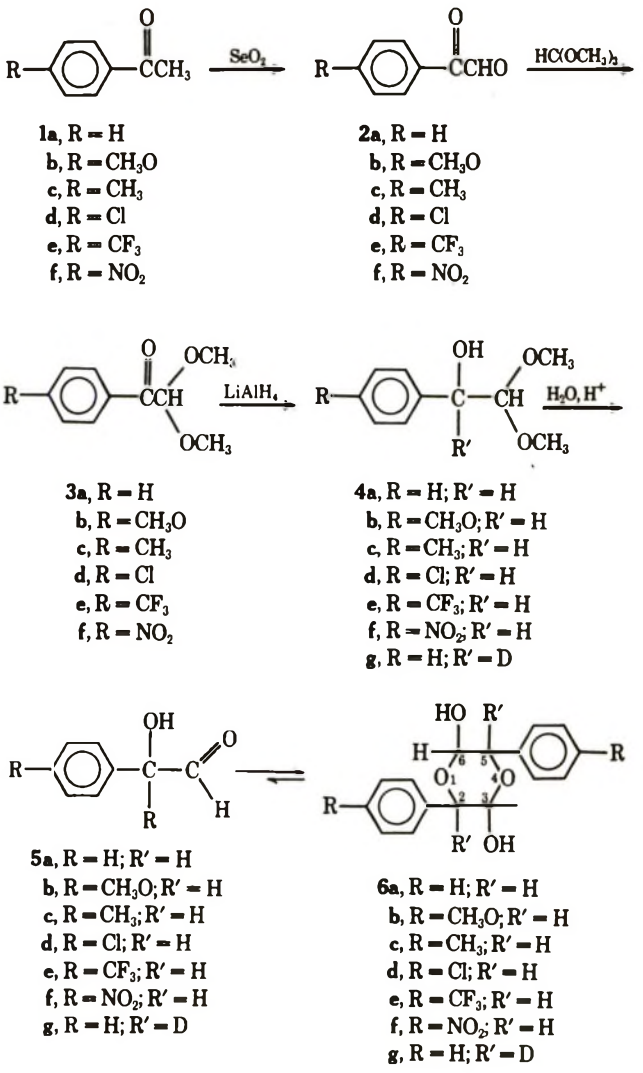


Figure 1.—Nmr spectra of mandelaldehyde dimers in DMSO-d_6: (A) freshly prepared dimer **6a**; (B) freshly prepared deuterated dimer **6g**; (C) aged dimer **6a**.

parent in the ir in the carbonyl region, in accord with the dimer structure **6a**. The nmr (see Figure 1) of freshly prepared samples of the dimer in dimethyl sulfoxide (DMSO-d_6) was rather simple, having a 10-proton multiplet for the aromatic protons, a 2-proton doublet for the protons at C-3 and C-6, a 2-proton doublet of doublets for the protons at C-2 and C-5, and a 2-proton doublet for the hydroxyl protons. Support for this interpretation was provided by the nmr spectrum (see Figure 1) of the C-3,C-6 dideuterio dimer **6g** (prepared by reducing **3a** with lithium aluminum deuteride), which displayed, in addition to the resonances arising from the aromatic ring, a pair of doublets with identical coupling constants. If, on the other hand, the sample of the dimer **6a** in DMSO-d_6 was allowed to stand at room temperature for several hours before spectral analysis, the spectrum was considerably more complex (see Figure 1), indicative of a mixture of isomers. In this spectrum, the resonance from the hydroxyl protons had become very broad.[6]

Para-substituted mandelaldehydes were prepared by the scheme outlined above for the parent compound. Only in the para nitro derivative case was the scheme modified with the substitution of sodium borohydride for lithium aluminum hydride in the reduction step.



1a, R = H
b, R = CH_3O
c, R = CH_3
d, R = Cl
e, R = CF_3
f, R = NO_2

2a, R = H
b, R = CH_3O
c, R = CH_3
d, R = Cl
e, R = CF_3
f, R = NO_2

3a, R = H
b, R = CH_3O
c, R = CH_3
d, R = Cl
e, R = CF_3
f, R = NO_2

4a, R = H; R′ = H
b, R = CH_3O; R′ = H
c, R = CH_3; R′ = H
d, R = Cl; R′ = H
e, R = CF_3; R′ = H
f, R = NO_2; R′ = H
g, R = H; R′ = D

5a, R = H; R′ = H
b, R = CH_3O; R′ = H
c, R = CH_3; R′ = H
d, R = Cl; R′ = H
e, R = CF_3; R′ = H
f, R = NO_2; R′ = H
g, R = H; R′ = D

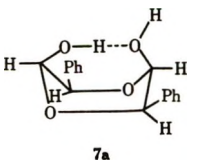
6a, R = H; R′ = H
b, R = CH_3O; R′ = H
c, R = CH_3; R′ = H
d, R = Cl; R′ = H
e, R = CF_3; R′ = H
f, R = NO_2; R′ = H
g, R = H; R′ = D

In all cases, the products were assigned the dimeric structure on the basis of the ir spectra.

Experimental Section[7]

Mandelaldehyde Dimer 6a.[8]—Following a published procedure,[9] acetophenone (**1a**) was converted in 80% yield to phenylglyoxal **2a**. A 112-g (0.84 mol) sample of this material was treated with a cooled solution of 300 ml of trimethyl orthoformate and 300 ml of methanol containing 5.6 g of ammonium chloride. After being stirred at room temperature for 24 hr the solution was cooled, diluted with 500 ml of 0.2 *N* ammonium hydroxide solution, and extracted four times with ether. The combined ether extract was processed in the usual fashion to yield, after distillation of the residue through a 75-cm spinning band column, 110 g (73%) of the dimethyl acetal **3a** as a pale yellow liquid: bp

(6) To account for these observations, it is conjectured that the dimer, in the solid state, exists in a boat conformation stabilized by transannular hydrogen bonds (**7**). In this conformation the magnetic environments of the



7a

ring protons are essentially insensitive to the configuration at C-3 and C-6, thus producing equivalent sets of hydrogens in the three diastereomers for which transannular hydrogen bonding is possible. If, then, this conformation is retained in freshly prepared solutions, the less complex spectrum is observed. In solution, however, the transannular hydrogen bond structure can eventually equilibrate with other conformations which may, in turn, interconvert to other configurations at C-2 and C-5 through ring-opened intermediates to produce a mixture of diastereomers in which the equivalence of the ring protons as well as the hydroxyl protons is lost. In this case, the more complex spectrum is observed.

(7) All melting points and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord spectrometer; uv spectra were recorded on a Cary Model 14 spectrometer; nmr spectra were recorded on a Varian Model A-60A spectrometer, and chemical shifts are reported in parts per million downfield shift from tetramethylsilane, used as an internal standard. The nmr spectrum of mandelaldehyde was obtained in degassed anhydrous hexadeuteriodimethyl sulfoxide solutions. The samples were prepared by placing a weighed amount of dry mandelaldehyde in an nmr tube fitted with a 10/30 standard taper joint. The tube was attached to a vacuum manifold, and after evacuation approximately 0.4 g of DMSO-d_6, previously degassed by at least three freeze–thaw cycles, was distilled into the sample tube through the all-glass system. The sample tube was then sealed off at 10^{-3} mm. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill., and by Mikroanalytisches Laboratorium, Vienna, Austria.

(8) We are indebted to Dr. D. W. Holty for carrying out exploratory experiments in this series.

(9) H. A. Riley and A. R. Gray, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 509.

TABLE I
YIELD AND ANALYTICAL DATA ON PARA-SUBSTITUTED MANDELALDEHYDE DIMERS

Para substituent	Yield of 4, %	Yield of 6, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N or X	Found, % C	Found, % H	Found, % N or X
CH_3O	60	53	148–150	$C_9H_{10}O_3$	65.05	6.07		65.10	6.13	
CH_3	58	37	148–150	$C_9H_{10}O_2$	71.98	6.71		72.13	6.79	
Cl	52	61	160–161	$C_8H_7ClO_2$	56.33	4.14	20.78	56.24	4.12	20.56
F_3C	45	20	159–162	$C_9H_7F_3O_2$	52.95	3.46	27.92	*a*		
NO_2	27	40	163–167	$C_8H_7NO_4$	53.04	3.90	7.73	53.14	4.04	7.14

[a] Satisfactory analyses could not be obtained for the *p*-trifluoromethylmandelaldehyde dimer **6e**, the results being consistently low in carbon and fluorine. Nmr analysis, however, indicated that a trifluoromethyl, rather than a difluoromethyl, group was present.

100–101° (4.5 mm) [lit.[10] bp 133° (16 mm)]; ir (liquid) 1700 (C=O) and 1120 cm^{-1} (CH_3OC); nmr (CCl_4) δ 3.40 (s, 6, CH_3O), 5.03 (s, 1, CH), 7.18–7.53 (m, 3, Ar H), and 8.03–8.20 ppm (m, 2, Ar H). To a stirred suspension of 28.5 g (0.75 mol) of lithium aluminum hydride in 600 ml of tetrahydrofuran, a solution of 77 g (0.43 mol) of **3a** in 75 ml of tetrahydrofuran was added, dropwise, over a period of 1 hr. After refluxing for 12 hr the reaction mixture was cooled to 0°, treated with water, and worked up in the usual way to yield, after distillation of the crude product through a 75-cm spinning band column, 62 g (80%) of mandelaldehyde dimethyl acetal (**4a**) as a colorless liquid: bp 80–82° (0.5 mm); ir (liquid) 3550 (OH), 2990 (CH_3), and 1130 cm^{-1} (CH_3OC); nmr ($CDCl_3$) δ 3.08 (s, 3, CH_3O), 3.28 (s, 4, CH_3O plus OH), 4.11 (d, 1, J = 6.5 Hz, H at C-2), 4.49 (d, 1, J = 6.5 Hz, H at C-1), and 7.12–7.38 ppm (m, 5, Ar H). A 62-g (0.34 mol) sample of this material was added to 1500 ml of 0.5 *N* hydrochloric acid, and the mixture was stirred at room temperature for 5 days. The precipitated solid was collected by filtration and washed, consecutively, with water and reagent grade acetone to yield 36 g (75%) of mandelaldehyde dimer **6a** as a white powder, mp 149–152°. Further purification was effected by acetone extraction of this material for 5 days in a Soxhlet apparatus, the material remaining in the extraction thimble being obtained as a white powder: mp 164–165° (lit.[5] 134–137°); ir (KBr) 3550 (OH) and 1140 cm^{-1} (COC); uv (95% ethanol) 248 nm (ϵ 106), 252 (151), 258 (192), 264 (147), and 295 (6); nmr (degassed DMSO-d_6) δ 5.20 (d of d, 2, J = 5.0 and 2.0 Hz, CHCHOH), 5.37 (d, 2, J = 2.0 Hz, CHCHOH), 6.30 (d, 2, J = 5.0 Hz, CHCHOH), and 7.21–7.59 ppm (m, 10, Ar H).

Anal. Calcd for $C_8H_8O_2$: C, 70.57; H, 5.92. Found: C, 70.35; H, 6.02.

Deuteromandeladehyde Dimer 6g.—Substituting lithium aluminum deuteride for lithium aluminum hydride, a 90-g sample of **3a** was reduced in the fashion described above to yield, after distillation through a 75-cm spinning band column, 78 g (87%) of **4g** as a colorless oil: bp 88–90° (1 mm); ir (liquid) 3590 (OH), 3000 (CH_3), and 2180 cm^{-1} (CD); nmr (CCl_4) 3.08 (s, 3, CH_3O), 3.28 (s, 4, CH_3O plus OH), 4.12 (s, 1, CH), and 7.10–7.37 (m, 5, Ar H). This was hydrolyzed and the crude product purified as described above to yield **6g** as a colorless powder: mp 164–165°; ir (KBr) 3550 (OH), 2180 (C–D), and 1140 cm^{-1} (COC); nmr (degassed DMSO-d_6) δ 5.20 (d, 2, J = 5.0 Hz, CDCHOH), 6.30 (d, 2, J = 5.0 Hz, CDCHOH), and 7.21–7.59 ppm (m, 10, Ar H).

Para-Substituted Mandelaldehyde Dimers 6b–f.—*p*-Methoxy-, *p*-methyl-, *p*-chloro-, and *p*-trifluoromethylmandelaldehyde dimers were prepared in a fashion identical with that described above for mandelaldehyde dimer itself. In the preparation of *p*-nitromandelaldehyde dimer (**6f**) the reduction of the keto acetal **3f** was accomplished with sodium borohydride. The optimum yields in these syntheses were realized without isolation of intermediate reaction products until the substituted mandelaldehyde dimethyl acetals **4b–f** were reached, at which point purification was accomplished by distillation through a 75-cm spinning band column. The yields of the mandelaldehyde dimethyl acetal and the mandelaldehyde dimer, along with analytical data on the latter, are recorded in Table I.

Registry No.—**3a**, 6956-56-5; **4a**, 21504-23-4; **4g**, 29568-40-9; **6a**, 21504-13-2; **6b**, 29568-41-0; **6c**, 29568-42-1; **6d**, 29568-43-2; **6e**, 29568-44-3; **6f**, 29568-45-4; **6g**, 29568-46-5.

Acknowledgment.—This work was supported, in part, by Grant No. 5 RO1 AM 02398 from the National Institutes of Health and Grant No. GP-11087X from the National Science Foundation to whom the authors express their gratitude.

(10) W. Madelung and M. E. Oberwegner, *Chem. Ber.*, **65**, 931 (1932)

The Reduction of Some Halocyclopropanes with Sodium Naphthalenide

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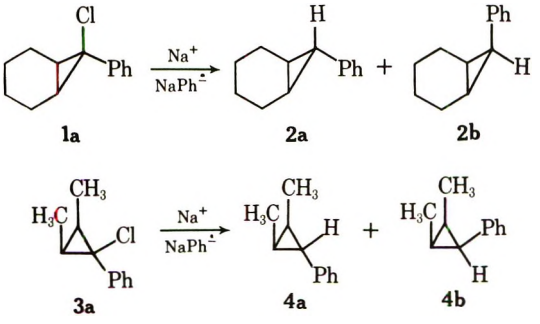
Herein we report some interesting solvent and temperature effects on the stereochemistry of the reduction of *anti*-7-phenyl-7-chloronorcarane (**1a**) and *anti*-1-phenyl-1-chloro-*cis*-2,3-dimethylcyclopropane (**3a**) with sodium naphthalenide (Scheme I).

SCHEME I



Compound **3a** was obtained in pure form by methods previously described.[2] Compound **1a** was synthesized by similar means (see Experimental Section) and has spectral and physical properties consistent with those reported by Schober.[3] The product ratios obtained in the reductions were determined by gas chromatography and are contained in Tables I and II.

We have defined as "dilute conditions" those reductions in which the reducing agent is added dropwise to a solution of the cyclopropyl halide, while "concen-

(1) Abstracted from the honors thesis of G. W. and the masters thesis of R. L. T., Middlebury College, 1970.
(2) D. B. Ledlie and S. MacLean, *J. Org. Chem.*, **34**, 1123 (1969).
(3) D. L. Schober, Ph.D. Thesis, University of Chicago, 1969.

TABLE I[a,b]
RELATIVE PERCENTAGES OF PRODUCTS OBTAINED IN THE REDUCTION OF 1a AND 3a WITH SODIUM NAPHTHALENIDE IN THF OR DME SOLVENT SYSTEMS

	Solvent (reagent solvent)	Room temp 2a	2b	4a	4b	−79° 2a	2b	4a	4b
	Dilute Conditions								
1	THF (THF)	64	36	86	14	83	17	92	8
2	DME (DME)	42	58	58	42				
	Concentrated Conditions								
3	THF (THF)	40	60	42	58	42	58	76	24
4	DME (DME)	40	60	58	42				

[a] Each entry is an average of at least two trials. In all cases data obtained in repeated runs differed by no more than 3%. [b] Absolute yields were between 80 and 100% for the reduction of 1a. Absolute yields were not determined for the reduction of 3a; however, in a similar study carried out in this laboratory which employed sodium biphenylide as the reducing agent yields averaged greater than 80%.

TABLE II[a]
RELATIVE PERCENTAGES OF PRODUCTS OBTAINED IN THE REDUCTION OF 1a AND 3a WITH SODIUM NAPHTHALENIDE IN DIETHYL ETHER SOLVENT SYSTEMS

	Solvent (reagent solvent)	Room temp 2a	2b	4a	4b	−79° 2a	2b	4a	4b
	Concentrated Conditions								
1	Et_2O (THF)	12	88	29	72	41	58	61	38
2	Et_2O (DME)	26	74	45	55				

[a] Each entry is an average of at least two trials. In all cases data obtained in repeated runs differed by no more than 3%.

trated conditions" are those in which the cyclopropyl halide is added to a solution of the reducing agent.[4]

As may be observed in Table I, the reductions carried out in tetrahydrofuran at −79° afforded a greater percentage of anti isomer than the corresponding reductions carried out at room temperature. In other words, as the temperature is lowered an increase in the thermodynamically more stable isomer results.[6] We feel that this occurs as a result of an increase in the concentration of the more stable cyclopropyl carbanion intermediate **6a** generated during the course of the reduction at this temperature. Several investigations which have

6a **6b**

= CH_3-, CH_3- or $-CH_2(CH_2)_2CH_2-$

a bearing on the mechanism of sodium naphthalenide and sodium biphenylide reductions of various organo halides have recently appeared.[5,7] From a perusal of these studies it seems quite clear that reductions of of alkyl bromides and chlorides with these reagents proceed *via* two, fast, one-electron transfers affording a carbanion which then abstracts a proton from solvent.

$$RX \xrightarrow{e} R\cdot + X^- \xrightarrow{e} R^- \xrightarrow{SH} RH$$

In addition, hydrogen abstraction from solvent by an intermediate radical does not seem to be a major competing reaction for the alkyl systems.[8] It is our contention that in the reduction of a system such as **1a** or **3a** a cyclopropyl radical is generated in which the barrier to inversion is quite low.[10,11] Thus, stereochemical integrity is quickly lost. A second electron is then rapidly added to generate the cyclopropyl carbanions **6a** and **6b** which because of the adjacent phenyl substituent are interconvertable. At the lower temperature there is a preponderance of **6a**, and as a result an increase in the percentage of the anti product is observed at this temperature.

If the reaction conditions are reversed (concentrated conditions, tetrahydrofuran), considerably more of the syn isomer is formed. It was observed that these reductions were much slower than for the corresponding dilute cases. Reactions carried out under the dilute conditions could be quenched immediately after the reducing agent had been added without effecting the yields of products. However, under the concentrated conditions the reaction mixture had to be stirred approximately 0.5 hr before starting material was completely consumed. This would imply that the halocyclopropanes are not soluble in the reducing medium, and perhaps the heterogeneous nature of the system and the more highly structured nature of the reducing medium as compared to the dilute cases places steric constraints upon the protonation process such that protonation from the less-hindered face of the carbanion is favored. This would result in more syn product.

In the dimethyoxyethane (DME) reductions, however, the product ratios are identical for both dilute and concentrated conditions. It might be argued that, due to the greater size of the DME molecule in comparison to that of THF, more of the syn product would be expected in the DME reductions and this is the overriding factor under both sets of reaction conditions. Further, one might expect to observe more of the syn product in reductions of **1a** than in the corresponding reductions of **3a** since the steric bulk of the methylene bridge in the carbanion derived from **1a** should tend to make protonation from the syn face of the molecule (resulting in anti product) less favorable than for the carbanion derived from **3a** which lacks a methylene bridge. In all cases tabulated in Table I this is observed.

Sodium naphthalenide has been shown to be unstable in diethyl ether; however, if enough THF and DME are present to adequately solvate the radical anion, solutions of the radical anion in THF–Et_2O or DME–Et_2O can be prepared.[12]

Several reductions were carried out employing solutions which were prepared by adding an excess of the reducing agent, dropwise, to 15 ml of anhydrous diethyl ether (see Table II). These solutions possessed the characteristic green color of the radical anion; however, their homogeneity is somewhat questionable since the

(4) The designation "dilute conditions" is not strictly correct since the reaction of the halide with the radical anion is very rapid and is probably over before the drop of reducing agent is completely dispersed.[5]

(5) S. J. Cristol and R. V. Barbour, *J. Amer. Chem. Soc.*, **90**, 2832 (1968).

(6) G. L. Gloss and R. A. Moss *ibid.*, **86**, 4042 (1969).

(7) (a) S. J. Cristol and R. W. Gleason, *J. Org. Chem.*, **34**, 1762 (1969); (b) J. F. Garst, P. W. Ayres, and R. C. Lamb, *J. Amer. Chem. Soc.*, **88**, 4260 (1966); (c) G. D. Sargent and M. W. Browne, *ibid.*, **89**, 2788 (1967); (d) G. D. Sargent, J. N. Cron, and S. Bank, *ibid.*, **88**, 5363 (1966); (e) J. Jacobs and D. Pensak, *Chem. Commun.*, 400 (1969).

(8) Walborsky and Chen have recently demonstrated in one case that a cyclopropyl radical is more reactive than an alkyl radical; thus, in our systems some hydrogen abstraction by an intermediate cyclopropyl radical may indeed be taking place.[9]

(9) H. M. Walborsky and J. Chen, *J. Amer. Chem. Soc.*, **92**, 7573 (1970).

(10) (a) R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963); (b) M. J. S. Dewar and M. Shanshall, *J. Amer. Chem. Soc.*, **91**, 3654 (1969).

(11) A planar species cannot be ruled out in this instance.

(12) N. D. Scott, J. F. Walker, and V. C. Hansley, *ibid.*, **58**, 2442 (1936).

concentration of THF or DME is initially too low to stabilize the radical anion and thus sodium and napthalene are probably formed to some extent. Of particular interest in Table II is the Et_2O (THF) system at room temperature which afforded considerably more of the syn product than did the THF (THF) system under comparable conditions (Table I). Again, one can envoke steric arguments in explaining these results; however, the probably nonhomogeneous nature of these solutions precludes a detailed picture of the protonation process.

It is evident from the data presented in Tables I and II that the stereochemistry of reduction for this type of system can be controlled by appropriate choice of reaction conditions. The problem of removing naphthalene and other aromatic by-products from the reaction mixture after a reduction has been carried out makes the synthetic worth of this technique somewhat questionable. In the systems here studied this was indeed a problem. However, one can envision phenylcyclopropane systems which are amenable to separation, and for these cases the technique has merit. Yields are usually high and cyclopropane cleavage products are not obtained. This is a serious drawback in the sodium–liquid ammonia reduction of cyclopropyl halides possessing a phenyl substitutent.

Experimental Section[13]

7-Phenyl-7-chloronorcarane (1a and 1b).—The compound was prepared in a 34% yield according to the method of Closs and Coyle.[14]

***anti*-7-Phenyl-7-chloronorcarane (1a).**—A mixture of the epimers **1a** and **1b** (27.3 g, 0.132 mol; 2/1 = **1a**/**1b**) and silver nitrate (8.99 g, 0.053 mol) in 50 ml of methanol was stirred for 24 hr. The reaction mixture was filtered, water and ether were added to the resulting solution, and the organic layer was separated. The reaction mixture was then worked up in the usual manner. Compound **1a** was separated from 7-phenyl-7-methoxynorcarane and 2-phenyl-3-methoxycycloheptene by column chromatography on silica gel and elution with ligroin. After five recrystallizations from pentane, 6.96 g of a white solid (mp 36–37°) was obtained. Spectral data and melting point were in complete agreement with those previously reported.[3]

***anti*-1-Phenyl-1-chloro-*cis*-2,3-dimethylcyclopropane (3a).**—The compound was prepared as previously described.[2]

Sodium Naphthalenide.—Sodium naphthalenide was prepared in both DME and THF according to the method of Scott.[12]

Sodium Naphthalenide Reductions.[15] Dilute Conditions.—To a solution of compound **1a** or **3a** (50 mg) in 15 ml of freshly dried DME or THF or ether was added dropwise with stirring approximately a twofold excess of sodium naphthalenide reagent (1.0 *M*). The reaction mixture was stirred for 5 min and quenched with water. An internal standard was added and the resulting mixture was analyzed by vpc (column a for the reduction of **1a** and column b for the reduction of **3b**).

Concentrated Conditions.—To a solution of 2 ml of reagent (1.0 *M*) in 15 ml of freshly dried DMF, THF, or ether was added with stirring neat or in solution approximately 50 mg of **1a** or **3b**. The reaction mixture was then stirred for 30 min. It was worked up and analyzed as described above.

Registry No.—**1a**, 6434-79-3; **3a**, 13154-00-2; sodium naphthalenide, 12521-84-5.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(13) Infrared spectra were determined with a Perkin-Elmer Model 137 or Model 457 recording spectrophotometer. All spectra were measured in carbon tetrachloride unless otherwise stated. The nmr spectra were measured at 60 Hz with an Hitachi Perkin-Elmer R20 spectrometer using tetramethylsilane as the internal reference. Columns used for gas chromatography (vpc) were (a) 10% Carbowax 20M 8 ft × 0.25 in. and (b) 20% DCQF1 12 ft × 1/8 in. All yields were determined by vpc. Unless otherwise stated, magnesium sulfate was employed as the drying agent. All reactions involving air or moisture sensitive compounds were carried out under a nitrogen atmosphere.

(14) G. L. Closs and J. J. Coyle, *J. Org. Chem.*, **31**, 2759 (1966).

(15) The reduction products were characterized by vpc retention times and comparison of infrared spectra with authentic samples. We thank Professor G. L. Closs for supplying us with the infrared spectra of compounds **2a** and **2b**.

Synthesis and Nuclear Magnetic Resonance Investigation of Some Fluorothiophenes

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Some years ago, we reported[1] the general synthesis of fluorine-containing thiophenes *via* the reaction of thienyllithiums with perchloryl fluoride. Recently renewed interest[2,3] in this reaction prompts us to report further work in this area. Fluorine derivatives of five-membered heterocycles have been only slightly investigated.[4] Recent evidence has indicated[5] that fluorine in the 2 position of thiophene has a stronger electron-withdrawing effect than in fluorobenzene. For these reasons, it became of interest to us to determine the position of electrophilic substitution and lithiation of 2-fluorothiophene.

Acylation of 2-fluorothiophene (**1**) with acetyl chloride and stannic chloride gave 5-fluoro-2-acetylthiophene (**2**). This ketone gave 5-fluoro-2-thenoic acid (**3**) upon treatment with sodium hypochlorite and base. Iodination of **1** by the iodine–mercuric oxide method and nitration, using nitric acid in acetic anhydride, also gave the corresponding 5-substituted products **4** and **5**. In all three of these examples, the products were 98% isomerically pure on the basis of nmr examination of the reaction mixture work-up. The assignment of substitution position was based on a comparison with recently observed coupling constants[2] for 2-fluorothiophene. In all cases, typical $J_{F\text{-}H_3}$ values of 1.4–2.1 Hz and $J_{H_3\text{-}H_4}$ values of 4.0–4.6 Hz were recorded (Table I).

Lithiation of 2-fluorothiophene with *n*-butyllithium followed by treatment with dimethylformamide gave 5-fluoro-2-thenaldehyde (**6**). The aldehyde was readily oxidized to **3** by silver oxide in base. The formation of **3** by this route as well as the observed nmr parameters for **6** (Table I) confirm the structure of the aldehyde.

(1) R. D. Schuetz, D. D. Taft, J. P. O'Brien, J. L. Shea, and H. M. Mork, *J. Org. Chem.*, **28**, 1420 (1963).

(2) S. Rodmar, B. Rodmar, M. K. Sharma, S. Gronowitz, H. Christiansen, and U. Rosen, *Acta Chem. Scand.*, **22**, 907 (1968).

(3) H. Christiansen, S. Gronowitz, B. Rodmar, S. Rodmar, J. Rosen, and M. K. Sharma, *Ark. Kemi.*, **30**, 561 (1969).

(4) Tetrafluorofuran is known but rapidly polymerizes at room temperature: J. Burdon, J. C. Tatlow, and D. F. Thomas, *Chem. Commun.*, 48 (1966). Tetrafluorothiophene is known and stable: J. Burdon, J. G. Campbell, I. W. Parsons, and J. C. Tatlow, *ibid.*, 27 (1969).

(5) Based on the difference in p*K* between 2-thenoic and 5-fluoro-2-thenoic acid: G. P. Nilles and R. D. Schuetz, *J. Org. Chem.*, in press.

TABLE I
COUPLING CONSTANTS FOR VARIOUS 2-SUBSTITUTED 5-FLUOROTHIOPHENES

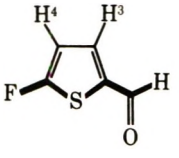
	R =	J_{FH_4}	J_{FH_3}	$J_{H_3-H_4}$
1[a]	H	1.62	3.07	3.89
2	$COCH_3$	1.4	3.6	4.2
3	COOH	1.8	4.0	4.0
4	I	2.1	3.6	4.1
5	NO_2	2.0	4.6	4.6
6	CHO	1.4	3.8	4.4

[a] Reference 2.

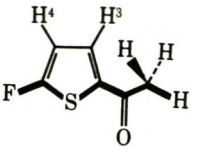
The $^1H-^{19}F$ coupling constant is known to increase in going from H_3 to H_5 in 2-fluorothiophene.[2] This effect is further exemplified in the quite large $^5J_{F\text{-}CHO}$ coupling constant of 4.2 Hz, determined in both the ^1H and ^{19}F nmr spectra. We therefore expected that the coupling between the fluorine and methyl protons in **2** might be observable. Indeed, this coupling was determinable and found to have a value of 0.45 Hz.

Karabatsos and Vane have shown[6] that H_3–CHO coupling in substituted benzaldehydes is observable only when the "W" effect (*i.e.*, H_3–CHO are trans–trans) is applicable. Thus, the principle rotamer in **6** would be the one in which the carbonyl function eclipses the sulfur atom. Further evidence was sought for this in the present work by variable temperature nmr observation of **6**. $J_{F\text{-}CHO}$ = 4.6 Hz for **6** in decalin between −34 and +42°. At 64°, J = 4.2 Hz, and at 89°, J = 3.9 Hz. Further increases in temperature up to 160° did not affect the coupling constant.[7,8]

These results are consistent with **7** representing the conformation of **6** and implies that **8** represents the con-



7



8

formation of **2** at room temperature and lower. Increasing the temperature serves to decrease this rotamer population as a consequence of overcoming the rotational energy barrier about the carbonyl carbon–thiophene ring bond. This results in a decrease in $J_{F\text{-}CHO}$ since the trans–trans coupling should be larger than the trans–cis coupling.[9]

While it is possible that some contribution to the magnitude of $J_{F\text{-}CHO}$ could arise from 6-bond coupling *via* the carbon skeleton, it was noted that no additional splitting of the aldehyde proton occurred at high temperature despite the trans–trans relationship between H_3 and CHO of the higher energy rotamer.[10] It would appear that coupling occurs through the sulfur ("W" effect) in both **2** and **6**.

(6) G. J. Karabatsos and F. M. Vane, *J. Amer. Chem. Soc.*, **85**, 3886 (1963).

(7) All coupling constants were determined at least three times each; the maximum deviation was ±0.05 Hz.

(8) This corresponds to a energy barrier (ΔEa^*_{298}) to rotation of ~16 kcal/mol. Other representative energy barriers for rotation about an sp^2–sp^2 single bond following: 2-furanaldehyde, 10–11 kcal; *p*-methoxybenzaldehyde, 9.2 kcal [J. P. Lowe, *Progr. Phys. Org. Chem.*, **6**, 1 (1968)].

(9) It was not possible to determine temperature effects on the nmr of **2** since the coupling approaches the limit of resolution of the instrument.

(10) This coupling is also absent in 2-thenaldehyde: S. Gronowitz and R. A. Hoffman, *Acta Chem. Scand.*, **13**, 1687 (1959).

Experimental Section

Melting points were determined on an Electrothermal melting point apparatus calibrated with furnished standards. Infrared spectra were recorded on a Perkin-Elmer 237B spectrophotometer between NaCl plates for liquids and as KBr disks for solids. The nmr spectra were recorded on a Varian A-56/60 instrument at ambient probe temperature and with Freon 112 as solvent and internal standard but referred to CCl_3F (Φ scale) and with TMS as internal standard for the proton spectra. Variable temperature nmr spectra were run in decalin. Analyses were by Galbraith Laboratories, Knoxville, Tenn.

5-Fluoro-2-thenaldehyde (6).—A solution of 70 ml of 1.6 *N* *n*-butyllithium (Foote Chemical Co.) was cooled to 3° and treated dropwise over a period of 1 hr with 10.2 g (0.100 mol) of 2-fluorothiophene in 50 ml of ether. To this 8.0 g (0.11 mol) of dimethylformamide in 40 ml of ether was added in 30 min. After an additional 1 hr of stirring, the mixture was poured into 100 g of ice and 50 ml of 6 *N* HCl. The organic layers were separated, and the aqueous layer was extracted with four 100-ml portions of ether. The combined, dried (Na_2SO_4) ether solutions were distilled to give 8.2 g (0.063 mol, 63%) of aldehyde: bp 60–61° (63 Torr); $n^{23}D$ 1.5482; ir 1680 cm^{-1} (C=O); pmr τ 0.18 (d, J = 4.2 Hz, CHO), 2.32 (d of d, J = 4.4, 3.8 Hz, H^3), 3.22 (d of d, J = 4.4, 1.4 Hz, H^4); fmr Φ 116.7 (m, J = 4.2, 3.8, 1.4 Hz).

A 2,4-dinitrophenylhydrazone prepared in the usual manner was recrystallized twice from ethanol for analysis, mp 257–258° dec.

Anal. Calcd for $C_{11}H_7O_4FN_4S$: C, 42.72; H, 1.96; N, 18.12; S, 10.37. Found: C, 42.64; H, 2.01; N, 17.96; S, 10.44.

5-Fluoro-2-thenoic Acid (3). A.—A mixture of 3 g of silver oxide and 2 g of sodium hydroxide in 40 ml of water was stirred and 1.30 g (0.0100 mol) of 5-fluoro-2-thenaldehyde was added in one portion. The mixture was stirred for 30 min and filtered. The filtrate was acidified to congo red with concentrated HCl. The precipitate of 5-fluoro-2-thenoic acid was collected and recrystallized from hot water: mp 146–148°; yield 0.70 g (0.0048 mol, 48%); ir 1680 cm^{-1} (C=O); pmr τ 0.52 (s, COOH), 2.83 (t, J = 4.0, 4.0 Hz, H^3), 3.31 (d of d, J = 4.0, 1.8 Hz, H^4).

Anal. Calcd for $C_5H_3FO_2S$: C, 41.08; H, 2.07; S, 21.94. Found: C, 41.14; H, 1.98; S, 21.77.

B. By the Haloform Reaction.—A mixture of 30 ml of 6% sodium hypochlorite, 20 ml of 5 *M* NaOH, and 1.30 g (0.0100 mol) of 5-fluoro-2-acetylthiophene was heated on the steam bath for 2 hr. The solution was cooled and acidified to congo red with concentrated HCl. The collected acid was recrystallized from water, yield 0.42 g (0.0029 mol, 29%). This material was identical by melting point, mixture melting point, and infrared spectra with that prepared in A.

5-Fluoro-2-acetylthiophene (2).—A mixture of 1.02 g (0.0100 mol) of 2-fluorothiophene and 0.87 g (0.011 mol) of acetyl chloride in 15 ml of CS_2 was cooled to 15° and treated dropwise with 2.87 g (0.011 mol) of stannic chloride with stirring in 1 hr. After an additional 1 hr of stirring, the mixture was poured into 10 ml of water. The organic layer was separated and the aqueous layer was extracted with two 20-ml portions of carbon disulfide. The combined, dried (Na_2SO_4) organic phases were stripped of solvent and the residue was vacuum distilled to give 1.15 g (0.0072 mol, 72%) of ketone: bp 80° (15 Torr); ir 1670 cm^{-1} (C=O); pmr τ 2.73 (d of d, J = 4.2, 3.6 Hz, H^3), 3.63 (d of d, J = 4.2, 1.4 Hz, H^4), 7.63 (d, J = 0.45 Hz, CH_3); fmr Φ 119.5, (m, J = 3.6, 1.4, 0.45 Hz).

A 2,4-dinitrophenylhydrazone prepared in the usual manner was recrystallized from ethanol for analysis, mp 246–248°.

Anal. Calcd for $C_{12}H_9FN_4O_4S$: C, 44.58; H, 2.49; N, 17.33; S, 9.92. Found: C, 44.46; H, 2.54; N, 17.21; S, 9.84.

5-Fluoro-2-iodothiophene (4).—A solution of 0.64 g (6.3 mmol) of 2-fluorothiophene in 5 ml of ether was treated with alternate portions of 1.1 g of yellow mercuric oxide and 1.6 g (6.3 mmol) of iodine with vigorous stirring, during 20 min, about 10% of each reagent being added at one time. The suspension of mercuric iodide was filtered off and washed with several portions of ether. The combined filtrate and washings were distilled to remove the solvent. The residue was subjected to micro molecular distillation at 60° (20 Torr) to give 0.88 g (3.9 mmol, 62%), of product: pmr τ 3.18 (d of d, J = 4.1, 3.6 Hz, H^3), 3.90 (d of d, J = 4.1, 2.1 Hz, H^4).

5-Fluoro-2-nitrothiophene (5).—A solution of 0.57 g (5.6 mmol) of 2-fluorothiophene in 5 ml of acetic anhydride was cooled to

0° with stirring. To this a solution of 0.77 g (1.0 mmol) of 90% nitric acid in 5 ml of acetic anhydride was added during 30 min. The reaction mixture was then stored at 0° for 24 hr and then poured into 50 g of ice and set aside at 0° for 24 hr. The solution was extracted with ether (two 25-ml portions) and the combined dried (Na_2SO_4) extracts were stripped of solvent. The residue was distilled at 80° (15 Torr) to give 0.72 g (4.9 mmol, 87%) of product: pmr τ 2.40 (t, J = 4.6, 4.6 Hz, H^3), 3.47 (d of d, J = 4.6, 2.0 Hz, H^4).

Anal. Calcd for $C_4H_2FNO_2S$: C, 32.63; H, 1.37; N, 9.52; S, 21.80. Found: C, 32.90; H, 1.61; N, 9.55; S, 22.01.

Registry No.—**2**, 29669-44-1; **2** 2,4-DNP, 29669-45-2; **3**, 4377-58-6; **4**, 29669-47-4; **5**, 29669-48-5; **6**, 29669-49-6; **6** 2,4-DNP, 29669-50-9.

Condensed 1,3-Benzothiazines. A Facile Rearrangement of 3-Alkyl-8-nitro-*s*-triazolo-[3,4-*b*](1,3,4)benzothiadiazepine

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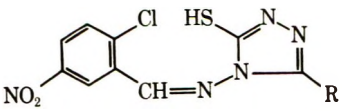
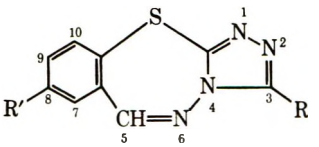
The fission of an N–N or of an N–O bond with formation of a cyano group under the influence of nucleophilic agents is well documented in five- and six-membered systems.[1] This note describes a novel example of a rearrangement in a seven-membered heterocyclic system involving fission of an N–N bond.

In connection with the synthesis of condensed *s*-triazole heterocycles described earlier,[2] 3-alkyl-4-(2-chloro-5-nitro)benzalamino-5-mercapto-*s*-triazoles were prepared by condensation of 3-alkyl-4-amino-5-mercapto-*s*-triazoles[3] with 2-chloro-5-nitrobenzaldehyde. It was reported earlier[2] that refluxing the sodium salt of the ethyl analog **1a** in dioxane gave 3-ethyl-8-nitro-*s*-triazolo[3,4-*b*](1,3,4)benzothiadiazepine (**2a**) as a yellow compound which showed in the nmr spectrum in DMSO-d_6 the azomethine proton as a singlet at δ 8.86. **2a** was also obtained by refluxing **1a** with 1 equiv of sodium ethoxide in ethanol.

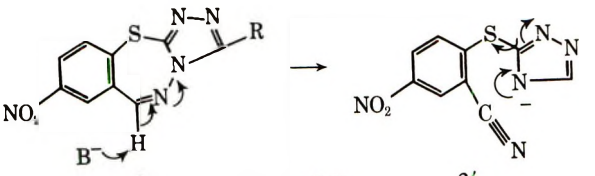
In the presence of 1.3–2.0 equiv of sodium ethoxide, **1a** gave a new product isomeric with **2a** as shown by analytical values and spectral data. The nmr spectrum showed no signal at δ 8.86 corresponding to the azomethine proton of **2a**; the ir spectrum contained an NH band at 3350 and 3260 cm^{-1} but no nitrile band. From these data, the product can be formulated as 3-ethyl-5-imino-7-nitro-5*H*-*s*-triazolo[3,4-*b*]-1,3-benzothiazine (**3a**). The course of the reaction from **1a** can be envisaged as involving the formation of **2a** which in the presence of base undergoes scission of the N–N bond to form the nitrile **2'a** which undergoes facile intramolecular ring closure to form **3a**. An alternative structure, 3-ethyl-5-imino-7-nitro-5*H*-*s*-triazolo[5,1-*b*]-1,3-benzothiazine (**3'a**) cannot be ruled out. Treatment of **2a** in presence of 0.3–1 equiv of sodium ethoxide in ethanol gave **3a** in 68% yield, showing that the reaction from **1a** proceeds through **2a** as an intermediate.



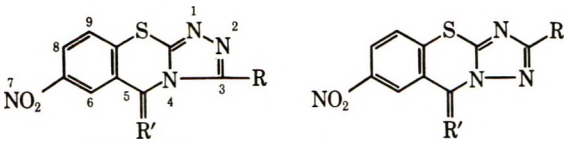
1a, R = C_2H_5
b, R = CH_3



2a, R = C_2H_5; R' = NO_2
b, R = CH_3; R' = NO_2
c, R = C_2H_5; R' = NH_2

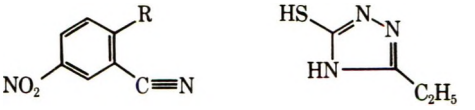


2 **2'a**, R = C_2H_5 **2'**
b, R = CH_3

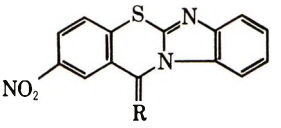


3 **3'**

3a, 3'a; R = C_2H_5; R' = NH
3b, 3'b; R = CH_3; R' = NH
3c, 3'c; R = C_2H_5; R' = NC(=O)CH_2Cl
3d, 3'd; R = C_2H_5; R' = O



4a, R = Cl **5**
b, R = OC_2H_5



6a, R = NH
b, R = O

Confirmation of the product as **3a** or **3'a** was obtained by establishing its identity with the condensation product of 2-chloro-5-nitrobenzonitrile[4] (**4a**) and 3-ethyl-5-mercapto-*s*-triazole[3] (**5**) in presence of sodium ethoxide. Under carefully controlled conditions of hydrolysis, **3a** gave **3d**, the corresponding oxo compound which showed the carbonyl band at 1710 cm^{-1} in the ir spectrum. This is in agreement with the reported values for fused cyclic lactams.[5] The chloroacetyl derivative **3c** and the oxo compound **3d** can have the alternative structures **3'c** and **3'd**.

(1) Yu. A. Naumov and I. I. Grandberg, *Russ. Chem. Rev.*, **35**, 9 (1966).
(2) T. George, R. Tahilramani, and D. A. Dabholkar, *Indian J. Chem.*, **7**, 959 (1969).
(3) H. Beyer and C. F. Kroger, *Justus Liebigs Ann. Chem.*, **637**, 135 (1960).
(4) J. J. Blanksma and P. G. Fohr, *Recl. Trav. Chim. Pays-Bas*, **65**, 706 (1946).
(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1957, p 205.

The methyl analog **1b** gave **2b** on refluxing with 1.1 equiv of sodium ethoxide in ethanol. Treatment of **2b** with 1 equiv of sodium ethoxide gave **3b** as the main product along with a low yield of 2-ethoxy-5-nitrobenzonitrile (**4b**) which was obviously formed by the action of sodium ethoxide on the intermediate nitrile **2'b**. Reduction of **2a** with Raney nickel gave **2c** which failed to undergo base-catalyzed rearrangement to a condensed 1,3-benzothiazine system, showing that the nitro group is essential for the rearrangement to occur.

As intramolecular amidine formation to give rise to condensed 1,3-benzothiazine system occurs in a facile way in the case of 4-amino-5-mercapto-*s*-triazoles, it was of interest to use other heterocyclic substrates containing the $-NHC(SH)=N-$ system. 2-Mercaptobenzimidazole was treated with 2-chloro-5-nitrobenzonitrile (**4a**) in presence of sodium ethoxide to give in good yield 6-imino-8-nitro-6*H*-benzimidazolo[2,3-*b*]-1,3-benzothiazine (**6a**). On treatment with ethanolic hydrochloric acid, the corresponding oxo compound **6b** was obtained, the carbonyl band of which appeared at 1702 cm^{-1} in the ir spectrum.

Experimental Section

Melting points are uncorrected. The ir spectra were examined as Nujol mulls on a Perkin-Elmer Model 421 spectrophotometer. The uv spectra in 95% ethanol were recorded on a Beckman DK-2A Model spectrophotometer and the nmr spectra were recorded on a Varian Associates A-60 spectrometer with TMS as internal standard.

3-Alkyl-4-(2-chloro-5-nitro)benzalamino-5-mercapto-*s*-triazoles.—The above compounds were prepared by refluxing together 1 equiv of 3-alkyl-4-amino-5-mercapto-*s*-triazole with 1.1 equiv of 2-chloro-5-nitrobenzaldehyde in 2-propanol containing 5 drops of concentrated HCl. The product was separated by filtration, washed with dilute sodium bicarbonate solution and water, and recrystallized from methanol.

4-(2-Chloro-5-nitro)benzalamino-3-ethyl-5-mercapto-*s*-triazole (**1a**) was obtained as yellow crystals in 80% yield: mp 236°; ir 1605 and 1588 cm^{-1}; uv max 250 nm (log ϵ 4.43) and 350 (3.62); nmr (CF_3COOH) 1.62 (t, 3 H, CH_2CH_3), 3.3 (q, 2 H, CH_2CH_3), 7.81 (d, 1 H, J = 9 Hz, aromatic), 8.40 (q, 1 H, J = 2.5 and 9 Hz, aromatic), 8.77 (d, 1 H, J = 2.5 Hz, aromatic), and 8.81 (s, 1 H, CH=N).

Anal. Calcd for $C_{11}H_{10}ClN_5O_2S$: C, 42.38; H, 3.23; N, 22.47; S, 10.55. Found: C, 42.63; H, 3.34; N, 22.21; S, 10.55.

4-(2-Chloro-5-nitro)benzalamino-5-mercpto-3-methyl-*s*-triazole (**1b**) was obtained as yellow crystals in 74% yield, mp 252°; ir and uv spectrum were similar to those of **1a**.

Anal. Calcd for $C_{10}H_8ClN_5O_2S$: C, 40.35; H, 2.71; N, 23.51. Found: C, 40.27; H, 2.80; N, 23.43.

3-Alkyl-8-nitrobenzo(7,8)-*s*-triazolo[3,4-*b*](1,3,4)thiadiazepines.—Equimolar amounts of 3-alkyl-4-(2-chloro-5-nitro)benzalamino-5-mercapto-*s*-triazoles and sodium ethoxide in ethanol were heated under reflux for 4 hr. The product was separated by filtration, washed with water, and recrystallized from methanol.

3-Ethyl-8-nitrobenzo(7,8)-*s*-triazolo[3,4-*b*](1,3,4)thiadiazepine (**2a**) was obtained as yellow crystals in 67% yield: mp 240°; ir 1605 and 1520 cm^{-1}; uv max 237 nm (log ϵ 3.24) and 278 (infl) (3.08); nmr (DMSO-d_6) δ 1.33 (t, 3 H, CH_2CH_3), 2.82 (q, 2 H, CH_2CH_3), 7.91 (d, 1 H, C-10 H), 8.41 (q, 1 H, C-9 H), 8.62 (d, 1 H, C-7 H), and 8.86 (s, 1 H, CH=N).

Anal. Calcd for $C_{11}H_9N_5O_2S$: C, 48.00; H, 3.30; N, 25.45. Found: C, 48.24; H, 3.52; N, 25.16).

3-Methyl-8-nitrobenzo(7,8)-*s*-triazolo[3,4-*b*](1,3,4)thiadiazepine (**2b**) was obtained in 70% yield: mp 275°; ir 1605 and 1520 cm^{-1}; uv max 233 nm (log ϵ 4.34) and 277 (infl) (4.03).

Anal. Calcd for $C_{10}H_7N_5O_2S$: C, 45.98; H, 2.70; N, 26.81. Found: C, 46.16; H, 2.92; N, 27.07.

3-Ethyl-5-imino-7-nitro-5*H*-*s*-triazolo[3,4-*b*]-1,3-benzothiazine (**3a**). **Method A. From 1a.**—To a solution of sodium (0.253 g, 12 mg-atoms) in ethanol (70 ml) was added compound **1a** (3.12 g, 0.01 mol). A crystalline solid began to separate when the reaction mixture was heated under reflux with stirring for 1 hr. The refluxing was continued for 4 hr, the reaction mixture cooled, and the product was filtered, washed with water and ethanol, and recrystallized from methanol to give **3a** as pale yellow crystals: yield 1.8 g (66%); mp 176°; ir 3350, 3260, and 1650 cm^{-1}; uv max 218 nm (log ϵ 4.48) and 320 (3.93); nmr (DMSO-d_6) δ 1.35 (t, 3 H, CH_2CH_3), 2.80 (q, 2 H, CH_2CH_3), 7.72 (d, 1 H, C-9 H), 8.43 (q, 1 H, C-8 H), and 9.50 (d, 1 H, C-6 H).

Anal. Calcd for $C_{11}H_9N_5O_2S$: C, 48.00; H, 3.30; N, 25.45. Found: C, 48.29; H, 3.43; N, 25.31.

Method B. From 2a.—Compound **2a** (8.25 g, 0.03 mol) was added to a solution of sodium (0.23 g, 10 mg-atoms) in ethanol (150 ml) and the reaction was carried out and worked up as above to obtain a yield of 5.6 g (68%).

Method C. From 4a and 5.—From **4a** (1.29 g, 0.01 mol) and **5** (1.83 g, 0.01 mol) using sodium ethoxide from sodium (0.25 g, 12 mg-atoms) in ethanol (60 ml) **3a** was obtained in 43.5% yield.

5-Imino-3-methyl-7-nitro-5*H*-*s*-triazolo[3,4-*b*]-1,3-benzothiazine (**3b**).—Compound **2b** (2.61 g, 0.01 mol) was added to ethanol (100 ml) to which sodium (0.23 g, 10 mg-atoms) had been added previously. The mixture was stirred and heated under reflux for 6 hr. The precipitate formed on cooling was filtered and recrystallized from ethanol to afford 0.8 g (31%) of **3b**: mp 191°; ir 3350, 3260, and 1645 cm^{-1}; uv max 218 nm (log ϵ 4.48) and 323 (3.93).

Anal. Calcd for $C_{10}H_7N_5O_2S$: C, 45.98; H, 2.70; N, 26.81. Found: C, 46.33; H, 2.91; N, 27.05.

The filtrate was concentrated under reduced pressure and cooled to give 80 mg of **4b** which on recrystallization from 2-propanol melted at 94°: ir 2240, 1600, 1580, 1030, and 750 cm^{-1}; uv max 296 nm (log ϵ 4.37) and 233 (infl) (4.21); nmr ($CDCl_3$) δ 1.51 (t, 3 H, CH_3), 4.33 (q, 2 H, OCH_2), 7.14 (d, 1 H, aromatic proton), and 8.45 (m, 2 H, aromatic protons).

Anal. Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.11; H, 4.39; N, 14.44.

3-Ethyl-5-(chloroacetyl)imino-7-nitro-5*H*-*s*-triazolo[3,4-*b*]-1,3-benzothiazine (**3c**).—To a stirred suspension of **3a** (2.75 g, 0.01 mol) in dry toluene (50 ml) containing pyridine (1 ml), a solution of chloroacetyl chloride (1.24 g, 0.01 mol) in toluene (10 ml) was added dropwise. The mixture was heated under reflux for 4 hr and cooled. The precipitated product was filtered and washed with water and ethanol. Recrystallization from methylene chloride–hexane gave 1.7 g (49.35%) of **3c** as colorless crystals: mp 218°; 1700 and 1650 cm^{-1}; uv max 323 nm (log ϵ 4.04) and 235 (infl) (3.96).

Anal. Calcd for $C_{13}H_{10}ClN_5O_3S$: C, 44.39; H, 2.87; N, 19.91. Found: C, 44.69; H, 3.16; N, 20.01.

3-Ethyl-7-nitro-5-oxo-5*H*-*s*-triazolo[3,4-*b*]-1,3-benzothiazine (**3d**).—Compound **3a** (1.37 g, 0.005 mol) was warmed with concentrated HCl (5 ml) and ethanol (10 ml). A homogeneous solution was formed and after 5 min the crystaline precipitate which was formed was filtered, washed with dilute sodium bicarbonate, and recrystallized from ethanol to give 0.3 g (22%) of **3d**: mp 193°; ir 1710 and 1610 cm^{-1}; uv max 236 nm (log ϵ 4.36) and 323 (3.81).

Anal. Calcd for $C_{11}H_8N_4O_3S$: C, 47.83; H, 2.92; N, 20.29. Found: C, 47.70; H, 3.17; N, 20.06.

7-Amino-3-ethyl-*s*-triazolo[3,4-*b*](1,3,4)benzothiadiazepine (**2c**).—A mixture of compound **2a** (4.0 g), Raney Nickel W-2 (2.5 g), and methanol (200 ml) was shaken with hydrogen at ambient temperature and atmospheric pressure until the absorption ceased which corresponded to absorption of nearly 3 mol of hydrogen. The suspension was filtered and the filtrate was evaporated to give a crystalline solid which melted at 160°. Recrystallization from ethanol gave 2.9 g (81%) of **2c** as yellow crystals: mp 181°; ir 3320 and 3200 cm^{-1}; uv max 246 nm (log ϵ 4.53).

Anal. Calcd for $C_{11}H_{11}N_5S$: C, 53.87; H, 4.52; N, 28.56. Found: C, 53.49; H, 4.86; N, 28.55.

Treatment of **2c** (2.45 g) with sodium ethoxide under conditions described for **2a** gave back unchanged material.

6-Imino-8-nitro-6*H*-benzimidazolo[2,3-*b*]-1,3-benzothiazine (**6a**).—The above compound was obtained in 65% yield from 2-mercaptobenzimidazole and 2-chloro-5-nitrobenzonitrile **4a** using sodium ethoxide under conditions described for **3a** and recrystallized from methanol: mp 287°; ir 3280, 1600, and 1580 cm^{-1}; uv max 225 nm (log ϵ 4.31), 245 (4.16), and 345 (3.63).

Anal. Calcd for $C_{14}H_8N_4O_2S$: C, 56.76; H, 2.72; N, 18.91. Found: C, 56.43; H, 2.89; N, 18.87.

8-Nitro-6-oxo-6*H*-benzimidazolo[2,3-*b*]-1,3-benzothiazine (**6b**).—Compound **6a** (1.48 g) was added to ethanol (15 ml) containing

concentrated HCl (8 ml) and heated under reflux with stirring for 4 hr. Filtration of the product followed by treatment with dilute sodium bicarbonate solution and ethanol gave yellow crystals of **6b**: yield 1.3 g (88%); mp >305°; ir 1702 and 1612 cm^{-1}; uv max 222 nm (log ϵ 4.26), 260 (4.35), and 335 (4.05).

Anal. Calcd for $C_{14}H_7N_3O_3S$: C, 56.57; H, 2.37; N, 14.14. Found: C, 56.86; H, 2.67; N, 13.90.

Registry No.—**1a**, 24848-32-6; **1b**, 29669-34-9; **2a**, 24848-33-7; **2b**, 29669-36-1; **2c**, 29913-47-1; **3a**, 29669-37-2; **3b**, 29669-38-3; **3c**, 29669-39-4; **3d**, 29669-40-7; **4b**, 29669-41-8; **6a**, 29669-42-9; **6b**, 29669-43-0.

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Synthesis of Pyrido[1,2-*a*]pyrimido[4,5-*b*]pyridine and Related Tricyclic Systems

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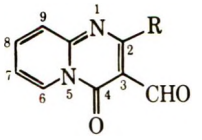
Contribution No. 217 from the CIBA Research Centre, Goregaon, Bombay-63, India

Received December 15, 1970

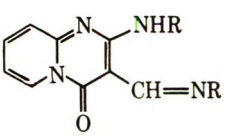
It has been reported earlier[1] that the pyrido[1,2-*a*]-pyrimidine nucleus can be functionalized by the Vilsmeier–Haack reaction to obtain 2-chloro-3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**1a**). We are describing below a facile synthesis of some tricyclic systems starting from **1a**.

Reaction of **1a** with methylamine and benzylamine took place exothermically to give the aldimines **2a** and **2b**. The nmr spectrum of **2a** showed the presence of the $CH{=}NCH_3$ moiety, the methyl as a doublet at δ 3.42, and the methine proton as a quartet at δ 8.78 ($J_{CH,NCH_3} = -1.6$ Hz);[2] **2b** showed the presence of the $CH{=}NCH_2C_6H_5$ moiety, the methylene group as a doublet at δ 4.72, and the methine proton as a triplet at δ 9.03 ($J_{CH,NCH_2} = -1.3$ Hz). Acid hydrolysis of **2a** gave the aldehyde **1b**. Treatment of **2a** with malononitrile gave in excellent yield 3-cyano-2-imino-1-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimido[4,5-*b*]pyridine (**3a**) which showed in the ir spectrum the imino group at 3300 cm^{-1} and the conjugated cyano group at 2210 cm^{-1}. In general, the formation of the above tricyclic system was very facile using compounds containing active methylene groups adjacent to a cyano group. Thus, ethyl cyanoacetate, cyanoacetamide, and benzoyl acetonitrile[3] reacted with **2a** to give compounds **3b–d** and benzoyl acetonitrile with **2b** to give **3e**. The course of the reaction can be envisaged to proceed through the addition of the anions of the above reagents followed by elimination of methylamine or benzylamine to give compounds **3a–e**. Aminoacetonitrile and cyanamide failed to react with **2a** and **2b**. Active methylene compounds such as acetylacetone, phenacyl chloride, or chloroacetone did not give tricyclic systems from **2a**, the only product which could be isolated and characterized being **1b**, the aldehyde corresponding to **2a**.

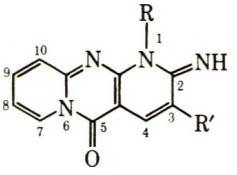
Methylhydrazine reacted with **2a** and **2b** to give the corresponding *N*-methylhydrazones **4a** and **4b**. On reaction with phosgene in toluene, **4a** gave a product



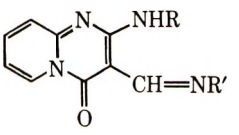
1a, R = Cl
b, R = $NHCH_3$



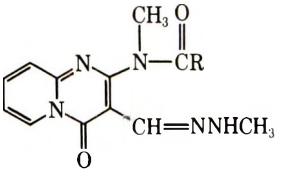
2a, R = CH_3
b, R = $CH_2C_6H_5$



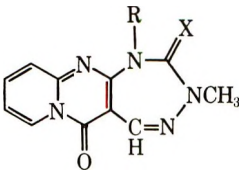
3a, R = CH_3; R′ = CN
b, R = CH_3; R′ = $COOC_2H_5$
c, R = CH_3; R′ = $CONH_2$
d, R = CH_3; R′ = COC_6H_5
e, R = $CH_2C_6H_5$; R′ = COC_6H_5



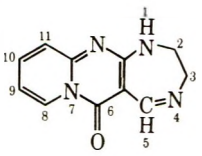
4a, R = CH_3; R′ = $NHCH_3$
b, R = $CH_2C_6H_5$; R′ = $NHCH_3$
c, R = CH_3; R′ = $N(CH_3)COCl$
d, R = CH_3; R′ = $N(CH_3)CO$-morpholine
e, R = $CH_2C_6H_5$; R′ = $N(CH_3)CSCl$
f, R = $CH_2C_6H_5$; R′ = $N(CH_3)CS$-morpholine
g, R = CH_3; R′ = $N(CH_3)COCOC_2H_5$



4c′, R = Cl
d′, R = morpholine



5a, X = O; R = CH_3
b, X = S; R = $CH_2C_6H_5$



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(1) E. A. Ingalls and F. D. Popp. *J. Heterocycl. Chem.*, **4**, 525 (1967).

(2) (a) K. Tori, M. Ohtsuru, and T. Kubota, *Bull. Chem. Soc. Jap.*, **39**, 1089 (1966); (b) W. Brugel, "Nuclear Magnetic Resonance Spectra and Chemical Structure," Academic Press, New York,-London, 1967, p 191.

(3) J. B. Dorsch and S. M. McElvain, *J. Amer. Chem. Soc.*, **54**, 2960 (1932).

which showed in the ir spectrum bands at 1740 and 1690 cm^{-1} and an identical uv spectrum in conformity with structure **4c**. Thiophosgene in toluene reacted with **4b** to give **4e** in an analogous way. **4c** and **4e** were surprisingly stable to aqueous alkali at ambient temperature but reacted with morpholine in refluxing dioxane to afford the morpholinoformyl derivative **4d** and the morpholinothioformyl derivative **4f**, respectively. The nmr spectrum of **4d** showed a doublet corresponding to the $NHCH_3$ group at δ 3.18 which coalesced to a singlet on addition of D_2O. Therefore, it is possible to rule out the alternate structures **4d'** for the morpholinoformyl derivative and **4c'** for its precursor, the chloroformyl derivative. **4d** underwent acid hydrolysis to give the aldehyde **1b**, providing confirmation of the structures **4d** and **4c** for the above derivatives. Attempts to cyclize **4c** and **4e** to obtain the pyrido[1,2-*a*]-pyrimido[4,5-*e*]-1,2,4-triazepine system **5a** and **5b** were unsuccessful. On treatment of **4a** with ethyl chloroformate, **4g** was obtained which resisted attempts at cyclization to give **5a**.

The β-chloroaldehyde **1a** reacted with ethylenediamine to give in good yield 1,2-dihydro-3*H*,6*H*-6-oxopyrimido[4,5-*e*]-1,4-diazepine **6**, whereas 2-chloro-5-nitrobenzaldehyde[4] on reaction with ethylenediamine failed to give any concrete results.[5]

Experimental Section

Melting points are uncorrected. The ir spectra were examined as Nujol mulls on a Perkin-Elmer Model 421 spectrophotometer. The uv spectra in 95% ethanol were recorded on a Beckman DK-2A Model spectrophotometer and the nmr spectra were recorded on a Varian A-60 spectrometer with TMS as internal standard. Thin layer chromatography (tlc) was performed on rilica gel G plates.

2-Chloro-3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**1a**) was prepared from 2,3-dihydro-2,4-dioxopyrido[1,2-*a*]pyrimidine by the Vilsmeier–Haack reaction in 76% yield, mp 226–227° (lit.[1] yield 39%, mp 224–226°).

2-Methylamino-3-(*N*-methyl)formimidoyl-4-oxo-4*H*-pyrido-[1,2-*a*]pyrimidine (**2a**).—To a stirred suspension of **1a** (4.0 g) in ethanol cooled to 10°, was added a saturated solution of methylamine in ethanol dropwise until a clear homogeneous solution was obtained. The reaction mixture which became exothermic was stirred for 2 hr. The yellow precipitate obtained was filtered and washed with water and 2-propanol. Recrystallization from ethanol gave 3.5 g of **2a** (85%): mp 154°; ir 3350, 1680, 1620, and 770 cm^{-1}; uv λ max 260 mμ (log ϵ 4.45), 352 (4.05); nmr ($CDCl_3$) δ 3.07 (d, 3 H, J = 6 Hz, $NHCH_3$), 3.42 (d, 3 H, J = −1.6 Hz, $CH{=}NCH_3$), 6.70–7.75 (m, 3 H, C-7, C-8, C-9 protons), 8.78 (q, 1 H, J = −1.6 Hz, $CH{=}NCH_3$), 8.80 (d, 1 H, C-6 H), 10.4 (s, broad, 1 H, NH). On addition of D_2O, the doublet at δ 3.07 coalesced to a singlet and the broad singlet at δ 10.4 disappeared.

Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.09; H, 5.59; N, 25.58. Found: C, 60.81; H, 5.66; N, 25.86.

2-Benzylamino-3-(*N*-benzyl)formimidoyl-4-oxo-4*H*-pyrido-[1,2-*a*]pyrimidine (**2b**) was obtained in an analogous way from **1a** and 3 equiv of benzylamine in 81% yield: mp 127° on recrystallization from ethanol; ir 3350, 1680, 1625, and 770 cm^{-1}; uv λ max 265 mμ (log ϵ 4.54), 358 (4.11); nmr ($CDCl_3$) δ 4.72 (d, 2 H, J = −1.3 Hz, $CH{=}NCH_2C_6H_5$), 4.80 (d, 2 H, J = 6 Hz, $NHCH_2C_6H_5$), 6.7–7.6 (m, 13 H, C-7, C-8, C-9, and phenyl protons), 8.86 (d, 1 H, C-6 H), 9.01 (t, 1 H, J = −1.3 Hz, $CH{=}NCH_2C_6H_5$), 11.25 (s, broad, 1 H, NH). On addition of D_2O, the doublet at δ 4.80 coalesced to a singlet and the singlet at δ 11.25 disappeared.

Anal. Calcd for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21. Found: C, 74.93; H, 5.62; N, 14.94.

2-Methylamino-3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**1b**).—A solution of **2a** (1.0 g) in ethanol (20 ml) containing 6 *N* HCl (0.5 ml) was refluxed for 0.5 hr. The product obtained on cooling was filtered, washed with water, and recrystallized from 2-propanol to give 0.3 g of **1b**: mp 220°; ir 3300, 1695, 1615, and 1590 cm^{-1}; uv λ max 252 mμ (log ϵ 4.28), 350 (3.99); λ infl 276 mμ (log ϵ 4.08); nmr (CF_3COOH) δ 3.45 (d, 3 H, $NHCH_3$) 7.75–8.20 (m, 2 H, C-7, C-8 protons), 8.62 (m, 1 H, C-9 proton), 9.46 (d, 1 H, C-6 H), 10.1 (s, 1 H, CHO), 10.59 (s, broad, 1 H, NH).

Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.10; H, 4.46; N, 20.68. Found: C, 59.01; H, 4.56; N, 20.57.

2-Imino-1-methyl-3-(substituted)-4-oxo-4*H*-1,2-dihydropyrido-[1,2-*a*]pyrimido[4,5-*b*]pyrimidines (**3a–d**). **3-Cyano Derivative 3a**.—To a solution of **2a** (2.03 g, 0.01 mol) in chloroform (15 ml) was added a solution of malononitrile (0.72 g, 0.011 mol) in chloroform and heated under reflux for 2 hr. The yellow crystalline product obtained was filtered and recrystallized from methanol–chloroform: yield 1.4 g (60%); mp 292°; ir 3300, 2210, and 1680 cm^{-1}; uv λ max 222 mμ (log ϵ 4.63), 272 (4.85), 4.03 (4.57); nmr (CF_3COOH) 4.35 (s, 3 H, NCH_3), 7.6–8.58 (m, 4 H, C-4, C-8, C-9, and C-10 protons), 9.28 (2 H, s, broad, C-7 and NH protons).

Anal. Calcd for $C_{13}H_9N_5O$: C, 62.14; H, 3.61; N, 27.88. Found: C, 61.68; H, 3.82; N, 27.58.

3-Carbethoxy derivative 3b was obtained from **2a** and ethyl cyanoacetate in 70% yield, mp 233° on recrystallization from chloroform–methanol.

Anal. Calcd for $C_{15}H_{14}N_4O_3$: C, 60.39; H, 4.73; N, 18.78. Found: C, 60.70; H, 4.81; N, 19.09.

3-Carboxamido derivative 3c was obtained from **2a** and cyanoacetamide in 63% yield, mp 320° on recrystallization from chloroform–methanol.

Anal. Calcd for $C_{13}H_{11}N_5O_2$: C, 57.98; H, 4.12; N, 26.01. Found: C, 58.27; H, 4.40; N, 25.80.

3-Benzoyl derivative 3d was obtained from **2a** and benzoyl acetonitrile in 67% yield: mp 262–263° from 2-propanol–methylene chloride; ir 3305, 1700, 1660, and 1580 cm^{-1}; uv λ max 252 mμ (log ϵ 4.43), 307 (4.14).

Anal. Calcd for $C_{19}H_{14}N_4O_2$: C, 69.08; H, 4.27; N, 16.96. Found: C, 68.77; H, 4.60; N, 16.81.

1-Benzyl-2-imino-3-benzoyl-4-oxo-4*H*-1,2-dihydropyrido[1,2-*a*]-pyrimido[4,5-*b*]pyrimidine (**3e**) was obtained from **2b** and phenacyl cyanide in 58% yield, mp 215° from chloroform–methanol.

Anal. Calcd for $C_{25}H_{18}N_4O_2$: C, 73.87; H, 4.46; N, 13.79. Found: C, 73.59; H, 4.65; N, 14.02.

2-Methylamino-3-(*N*-methyl)aminoformimidoyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**4a**).—Methylhydrazine (1.01 g, 0.022 mol) in ethanol (10 ml) was added to **2a** (4.32 g, 0.02 mol) and stirred under reflux for 2 hr. The precipitate obtained was filtered and recrystallized from methanol to afford 4.1 g (94%) of **4a**: mp 210°; ir 3260, 1655, and 1605 cm^{-1}; uv λ max 264 mμ (log ϵ 4.47); nmr ($CDCl_3$ + CD_3SOCD_3) δ 2.90 (s, 3 H, $=NNHCH_3$), 3.15 (d, 3 H, $NHCH_3$), 6.9–7.6 (m, 3 H, C-7, C-8, and C-9 protons), 8.22 (s, 1 H, CH=N), 8.86 (d, 1 H, C-6 proton).

Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67; N, 30.29. Found: C, 57.42; H, 5.87; N, 30.18.

2-Benzylamino-3-(*N*-methyl)aminoformimidoyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**4b**) was obtained in 61% yield from **2b** under conditions described for **4a**, mp 156° on recrystallization from methanol.

Anal. Calcd for $C_{17}H_{17}N_5O$: C, 66.43; H, 5.58; N, 22.79. Found: C, 66.80; H, 5.66; N, 23.00.

***N*-Chloroformyl derivative 4c** was obtained in 74% yield by refluxing **4a** with excess of phosgene in toluene: mp 226° on recrystallization from CH_2Cl_2–hexane; ir 1720, 1695, and 1615 cm^{-1}; uv λ max 262 mμ (log ϵ 3.92).

Anal. Calcd for $C_{12}H_{12}ClN_5O_2$: C, 49.07; H, 4.12; N, 23.84. Found: C, 49.18; H, 4.18; N, 23.80.

***N*-(Morpholinoformyl) derivative 4d** was obtained by treatment of **4c** with morpholine in dioxane in 66% yield: mp 193° on recrystallization from methylene chloride; ir 3290, 1680, and 1630 cm^{-1}; uv λ max 262 mμ (log ϵ 4.51); nmr ($CDCl_3$) δ 3.18 (d, 3 H, $NHCH_3$), 3.35 (s, 3 H, $=NNCH_3$), 3.55 (m, 4 H, NCH_2), 3.72 (m, 4 H, OCH_2), 6.85–7.75 (m, 3 H, C-7, C-8, and C-9 protons), 8.26 (s, 1 H, CH=N), 8.86 (d, 1 H, C-6 proton), and 8.95 (s, 1 H, NH).

Anal. Calcd for $C_{16}H_{20}N_6O_3$: C, 55.80; H, 5.85; N, 24.41. Found: C, 55.61; H, 5.71; N, 24.09.

Acid Hydrolysis of 4d to 1b.—A solution of **4d** (0.5 g) in ethanol (15 ml) containing 2 *N* HCl (5 ml) was refluxed for 1 hr.

(4) H. Erdmann, *Justus Liebigs Ann. Chem.*, **272**, 148 (1892).

(5) Unpublished observations by authors.

The solvent was removed under reduced pressure to give a residue which was treated with water to give 0.2 g of a product which melted at 219° on recrystallization from 2-propanol and was identical with **1b** described above by mixture melting point, spectral comparison, and tlc behavior.

N-**Thioformyl derivative 4e** was obtained in 71% yield by refluxing **4b** with thiophosgene in toluene: mp 236° on recrystallization from methylene chloride–ether; ir 3250, 1660, and 1610 cm^{-1}.

Anal. Calcd for $C_{18}H_{16}ClN_5OS$: C, 56.03; H, 4.18; N, 18.15. Found: C, 56.21; H, 4.36; N, 17.86.

N-**Morpholinothioformyl derivative 4f** was obtained in 56% yield from **4e** and morpholine, mp 166° on recrystallization from methylene chloride–ether.

Anal. Calcd for $C_{22}H_{24}N_6O_2S$: C, 60.54; H, 5.54; N, 19.26. Found: C, 60.76; H, 5.52; N, 19.22.

2-Methylamino-3-(*N*-carbethoxy-*N*-methyl)aminoformimidoyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (4g).—To a suspension of **4a** (2.31 g, 0.01 mol) in dioxane (80 ml) containing pyridine (0.8 g) was added ethyl chloroformate (1.08 g, 0.01 mol) and the mixture was heated with stirring under reflux for 4 hr. The precipitate obtained on cooling was filtered and recrystallized from methylene chloride to give 1.8 g of **4g**: mp 190°; ir 3510, 1680, and 1660 cm^{-1}; uv λ max 260 mμ (log ε 4.48).

Anal. Calcd for $C_{14}H_{17}N_5O_3$: C, 55.43; H, 5.65; N, 23.09. Found: C, 55.16; H, 6.17; N, 22.91.

6-Oxo-3*H*,6*H*-1,2-dihydropyrimido[4,5-*e*]-1,4-diazepine (6).—Ethylenediamine (3.6 g, 0.06 mol) was added to a stirred suspension of **1a** (4.16 g, 0.02 mol) in dioxane (50 ml) and heated under reflux for 4 hr. The precipitate obtained on cooling was filtered and washed with water and ethanol. On recrystallization from chloroform–dioxane 2.9 g (78%) of product was obtained: mp 310°; ir 1680, 1610, and 1460 cm^{-1}; uv[6] λ max 217 and 265 mμ; nmr (CF_3COOH) δ 4.25 (s, broad, 4 H, $NHCH_2$ and $=NCH_2$), 7.3–7.7 (m, 3 H, C-9, C-10, and C-11 protons), 8.32 (m, 1 H, CH=N), 9.03 (d, 1 H, C-8 proton).

Anal. Calcd for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 25.97. Found: C, 61.49; H, 4.75; N, 25.77.

Registry No.—**1b**, 29494-74-4; **2a**, 29494-75-5; **2b**, 29494-76-6; **3a**, 29494-77-7; **3b**, 29494-78-8; **3c**, 29494-79-9; **3d**, 29494-80-2; **3e**, 29494-81-3; **4a**, 29494-82-4; **4b**, 29494-83-5; **4c**, 29494-84-6; **4d**, 29494-85-7; **4e**, 29494-86-8; **4f**, 29494-87-9; **4g**, 29494-88-0; **6**, 29494-89-1.

Acknowledgment.—Thanks are expressed to Dr. T. R. Govindachari for his interest in the above work and Dr. S. Selvavinayakam for analytical and spectral data.

(6) Only qualitative assay could be performed owing to the high degree of insolubility of the compound in solvents.

Syntheses and Cis–Trans Isomerization of Light-Sensitive Benzenediazo Sulfides

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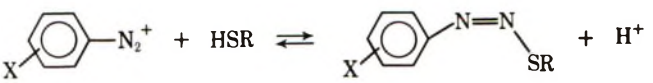
Although until recently benzenediazoalkyl sulfides were considered highly decomposable,[1] Van Zwet and Kooyman succeeded in preparing benzenediazo-*tert*-butyl sulfide and its 2,4,6-trimethyl derivative and in determining the cis–trans isomerization and other physical properties.[2] We were unable to prepare other derivatives by the same method but found a more general synthesis which is presented in the Experimental Section. In this way a number of new derivatives were synthesized and studied, especially in view of their applicability in photographic physical development systems, a subject extensively discussed elsewhere.[3] For photographic applications the very slow thermal cis-to-trans isomerization and the stability of the cis isomer are important properties which were also helpful in studying the synthesis. The reaction was found to depend on the equilibrium between diazonium ion **1** and benzene-*cis*-diazo sulfide **2**. The substituents X



1 **2**

appear to determine the quantity of cis isomer **2** formed when the reactants **1** and thiol are brought together. The solution of the reactants showed, *e.g.*, when X was 3,5-Cl_2-4-$N(CH_3)_2$, immediately the absorption spectrum of the cis isomer **2** which must mean according to empirical determinations that there was at most 4% diazonium left. A dilute solution of H_2SO_4 had to be added to move the equilibrium to the left which produced the diazonium spectrum. On the other hand, when, *e.g.*, X was 2,5-$(OCH_3)_2$-4-(4′-tolylmercapto), a compound photographically uninteresting and therefore not extensively studied, the diazonium spectrum was observed which changed to the cis spectrum if NaOH solution was added to move the equilibrium to the right. Generally, when the NaOH solution was added too rapidly, the diazonium salt decomposed with the formation of nitrogen. Optimum yields of pure cis isomers were obtained when the NaOH solution was slowly added to give a final pH of 6.

The final step in the synthesis is the thermal isomerization of the cis isomers to obtain the photographically applied trans isomers. We found that the thermal isomerization in benzene, the solvent chosen by Van Zwet and Kooyman,[2] even in yellow safe-light was accompanied by decomposition. Much purer products were obtained by heating in isooctane at 90° for 2 hr.

The data in Table I were calculated from 5 to 12 points by the method of least squares. The deviations are standard deviations. The correlation coefficients were all better than 0.99. Frequency factors *f*

TABLE I

THERMAL CIS-TO-TRANS ISOMERIZATION RATE CONSTANTS *k* IN ETHANOL AT 60° FOR BENZENEDIAZO SULFIDES ($C_6H_5N_2SR$) WITH SUBSTITUENTS X ATTACHED TO THE BENZENE RING[a]

X	R	10^4k, sec^{-1}	Log *f*	*A*, kcal/mol
4-NO_2	*tert*-Butyl	0.52 ± 0.01	12.4 ± 0.7	25.3 ± 1.0
2-Cl-4-NO_2	*tert*-Butyl	0.83 ± 0.01	11.7 ± 0.7	24.0 ± 1.1
4-CN	*tert*-Butyl	0.48 ± 0.01	18.3 ± 0.9	28.8 ± 1.3
4-Cl	*tert*-Butyl	0.39 ± 0.04	11.2 ± 1.0	23.8 ± 1.6
4-NO_2	*tert*-Octyl	1.40 ± 0.01	12.2 ± 0.4	24.4 ± 0.6
4-NO_2	$C(C_6H_5)_3$	35 ± 2	11.7 ± 0.3	21.5 ± 0.5

[a] Frequency factors *f* and activation energies *A*.

(1) R. Pütter in "Methoden der Organischen Chemie," Houben-Weyl, Georg Thieme Verlag, Stuttgart, 1965, p 567, band 10/3.

(2) H. van Zwet and E. C. Kooyman, *Recl. Trav. Chim. Pays-Bas*, **86**, 993 (1967).

(3) H. Jonker, C. J. Dippel, H. J. Houtman, C. J. G. F. Janssen, and L. K. H. van Beek, *Photogr. Sci. Eng.*, **13**, 1 (1969).

TABLE II

TRANS AND CIS ISOMERS OF SUBSTITUTED BENZENEDIAZO SULFIDES, $C_6H_5N_2SR$[a]

R	X	Isomer	Uv, nm (ε)	Nmr chemical-shift values: $C(CH_3)_3$	$C(C_6H_5)_3$	C_6H_4	C_6H_3	C_6H_2	Other
$C(CH_3)_3$	4-NO_2	Trans	351 (20,000)	1.66		7.61, 8.27			
		Cis		1.61		7.10, 8.33			
$C(CH_3)_3$	2-Cl-4-NO_2	Trans	356 (17,000)	1.67			7.31, 8.08, 8.32		
		Cis		1.64					
$C(CH_3)_3$	4-Cl	Trans	332 (17,700)	1.62		7.34, 7.40			
$C(CH_3)_3$	4-Cl-2-CH_3	Trans	334 (13,500)	1.65			7.13		2.52 (CH_3)
		Cis		1.60			7.13		2.05 (CH_3)
$C(CH_3)_3$	4-CN	Trans	338 (19,000)	1.65		7.62			
		Cis		1.61		7.08, 7.75			
$C(CH_3)_3$	3,5-Cl_2-4-$N(CH_3)_2$	Trans	348 (12,700)	1.63				7.39	2.91 ($N(CH_3)_2$)
		Cis		1.61				7.03	2.93 ($N(CH_3)_2$)
tert-Octyl	4-NO_2	Trans	355 (19,800)						
Adamantyl	4-NO_2	Trans	345 (19,200)						
$C(C_6H_5)_3$	4-NO_2	Trans	356 (19,900)		7.25[b]	7.09, 7.20, 8.04, 8.18[b]			
		Cis			7.22[b]	6.98, 7.13, 8.16, 8.31[b]			
$C(C_6H_5)_3$	4-Cl	Trans	338 (18,800)						
$C(C_6H_5)_3$	3-Cl-4-$N(CH_3)_2$	Trans	368 (20,500)						

[a] X = substituents on the benzene ring. [b] Data reported by Van Zwet and Kooyman.[2]

TABLE III

SUBSTITUTED BENZENEDIAZO SULFIDES, $C_6H_5N_2SR$[a]

R	Registry no. Cis	Registry no. Trans	X	Mp, °C	Calcd, % C	H	N	S	Cl	Found, % C	H	N	S	Cl
$C(CH_3)_3$	29577-81-9	29577-82-0	4-NO_2	60–62	50.20	5.47	17.56	13.40		50.3	5.2	17.7	13.4	
$C(CH_3)_3$	29577-83-1	29577-84-2	2-Cl-4-NO_2	76.5–77	43.89	4.42	15.53	11.71	12.95	43.9	4.4	15.5	11.8	13.2
$C(CH_3)_3$		29577-85-3	4-Cl	47–49	52.51	5.73	12.25	14.02	15.50	52.4	5.7	12.9	14.1	15.4
$C(CH_3)_3$	29577-86-4	29577-87-5	4-Cl-2-CH_3	40–42	54.42	6.23	11.54	13.21	14.60	53.1	6.3	11.6	13.4	14.9
$C(CH_3)_3$	29577-88-6	29577-89-7	4-CN	104–106	60.25	5.97	19.16	14.62		59.9	5.8	19.5	14.8	
$C(CH_3)_3$	29577-90-0	29577-91-1	3,5-Cl_2-4-$N(CH_3)_2$	47–49	47.06	5.59	13.72	10.47	23.15	46.8	5.8	13.9	9.8	23.5
tert-Octyl		29577-92-2	4-NO_2	62–64	56.92	7.17	14.22	10.85		56.3	6.9	13.7	11.1	
n-Adamantyl		29577-93-3	4-NO_2	148–150										
$C(C_6H_5)_3$			4-NO_2	143–145 dec[b]	70.58	4.51	9.88	7.52		70.1	4.5	10.0	7.6	
$C(C_6H_5)_3$		27843-80-7	4-Cl	125–126 dec	72.36	4.61	6.75	7.73	8.54	72.3	4.9	6.8	7.7	8.55
$C(C_6H_5)_3$		29577-95-5	3-Cl-4-$N(CH_3)_2$	135 dec	70.81	5.28	9.17	6.99	7.74	70.3	5.2	9.25	7.1	7.8

[a] X = substituents on the benzene ring. [b] Van Zwet and Kooyman[2] found 145° dec

and activation energies were derived from $k = f \exp(-A/RT)$ between 20 and 70°. Substituents on the benzene ring had little influence on the rate of cis-to-trans isomerization, unless obviously ortho to the diazo group, *e.g.*, when X was 2-Cl-4-NO_2. The isomerization rates increased when bulkier groups R were attached to the sulfur atom, but the activation energies decreased as expected.

Van Zwet and Kooyman[2] gave two possible mechanisms for the thermal cis-to-trans isomerization, namely *via* rotation about the N–N bond or *via* ionization and recombination. For azobenzene derivatives, Talaty and Fargo[4] proposed a third mechanism with a linear transition state in which one or both nitrogen atoms undergo a change in hybridization to the sp state. The arguments for this third mechanism were the low activation energies of 21–24 kcal/mol in combination with the absence of large solvent effects. Since the benzenediazo sulfides of Table I have activation energies of 21–28 kcal/mol and generally small solvent effects,[2] the same mechanism of thermal cis-to-trans isomerization *via* a linear transition state seems to hold.

The effect of substituents X on the absorption spectra (Table II) also suggests a resemblance to azobenzenes. Both classes of compounds have the main absorption peaks of the 4-NO_2 derivatives considerably shifted to the visible with respect to the unsubstituted compounds. This has been attributed to polar resonance structures,[5] but the solvent effects are not entirely consistent with that interpretation. The main absorption peak of 4-nitro-benzenediazo-*tert*-butyl sulfide was found at 351 nm in ethanol but at 388 nm in benzene. Similar effects were reported in ref 2.

Experimental Section

The purity of the cis and trans benzenediazo sulfides was tested by silica gel thin layer chromatography with cyclohexane eluent and by nmr and ir. The nmr spectra were recorded in our analytical department by Mr. H. M. van den Bogaert on a Varian A-60 spectrometer in carbon tetrachloride with tetramethylsilane as internal standard. Analyses were performed by the TNO Organic Chemistry Institute at Utrecht. In the synthetic work assistance was given by Mr. Th. C. J. M. Hegge. The absorption spectra were recorded with a Unicam SP800 spectrophotometer, the triphenylmethyl sulfides in ethyl acetate, the others in 98% ethanol. Isomerization rate constants were determined by photoisomerizing the ethanolic solutions of the trans isomers at 405 nm and spectrophotometrically following the thermal reverse isomerization from the resultant cis isomer to the trans form. The stoppered cells were placed in a constant temperature housing. Since both isomers are light-sensitive, the experiments were carried out in yellow safe-light to prevent photoisomerization.

Anilines and Diazonium Tetrafluoroborates.—Most of the anilines were commercial products. Two of them, 3-Cl-4-$N(CH_3)_2$-aniline and 3,5-Cl_2-4-$N(CH_3)_2$-aniline, were prepared by known methods[6,7] which were improved in that the $N(CH_3)_2$ group was introduced by passing gaseous $HN(CH_3)_2$ into the solution of the bromobenzene derivative in dimethylformamide.[8] The diazonium boron tetrafluorides were prepared as reported earlier.[8]

Benzenediazo Sulfides.—The benzenediazoalkyl sulfides were obtained as follows. The alkylthiol (0.1 mol) was added to a solution of 0.1 mol of diazonium·BF_4 in 250 ml of acetone cooled to 0°. The pH was adjusted with the help of pH paper to a value of between 5 and 6 adding dropwise about 160 ml of 2.5% aqueous NaOH in about 1 hr.

If the cis isomer did not crystallize it was extracted with benzene. The extract was dried (Na_2SO_4) and the solvent removed at reduced pressure at 20°. The residual product was dissolved in 250 ml of isooctane. If the cis isomer did crystallize, it was directly dissolved in isooctane. The solution was kept at 90° for 2 hr to achieve the cis-to-trans isomerization. The solvent was removed at reduced pressure. The crude products were recrystallized from ethanol, yields 50–80% (Table III).

The benzenediazotriphenylmethyl sulfides were prepared by the method given in ref 2 (p 1004).

(4) E. R. Talaty and J. C. Fargo, *Chem. Commun.*, 65 (1967).
(5) W. G. B. Huysmans, Thesis, Leiden, 1964, p 34.
(6) E. E. Ayling, J. H. Gorvin, and L. E. Hinkel, *J. Chem. Soc.*, 755 (1942).
(7) A. van Loon, P. E. Verkade, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **79**, 977 (1960).
(8) L. K. H. van Beek, J. Boven, and J. Helfferich, *ibid.*, **87**, 737 (1968).

Base-Catalyzed Reaction of Methyl α-Cyano-β-(2-thienyl)acrylate

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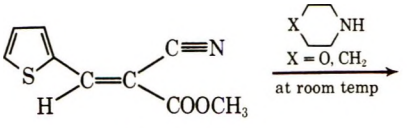
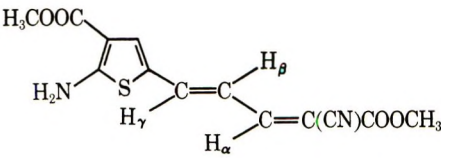
In extension of our previous studies on base-catalyzed ring opening–closure reaction of α-cyano-β-furylacrylic esters, which led to the formation of γ-(4-alkoxycarbonyl-5-aminofuryl)acroleins,[2] we wish to report the one-step synthesis of rather complex thiophenes. When methyl α-cyano-β-(2-thienyl)acrylate (**1**) was allowed to stand overnight in morpholine or in piperidine at room temperature, a colored product resulted in 56 and 69% yields, respectively. The product obtained was assigned as the structure of methyl 2-cyano-5-(4-methoxycarbonyl-5-amino-2-thienyl)-2,4-pentadienoate (**2**), on the basis of ir, nmr, and mass spectral data.



1

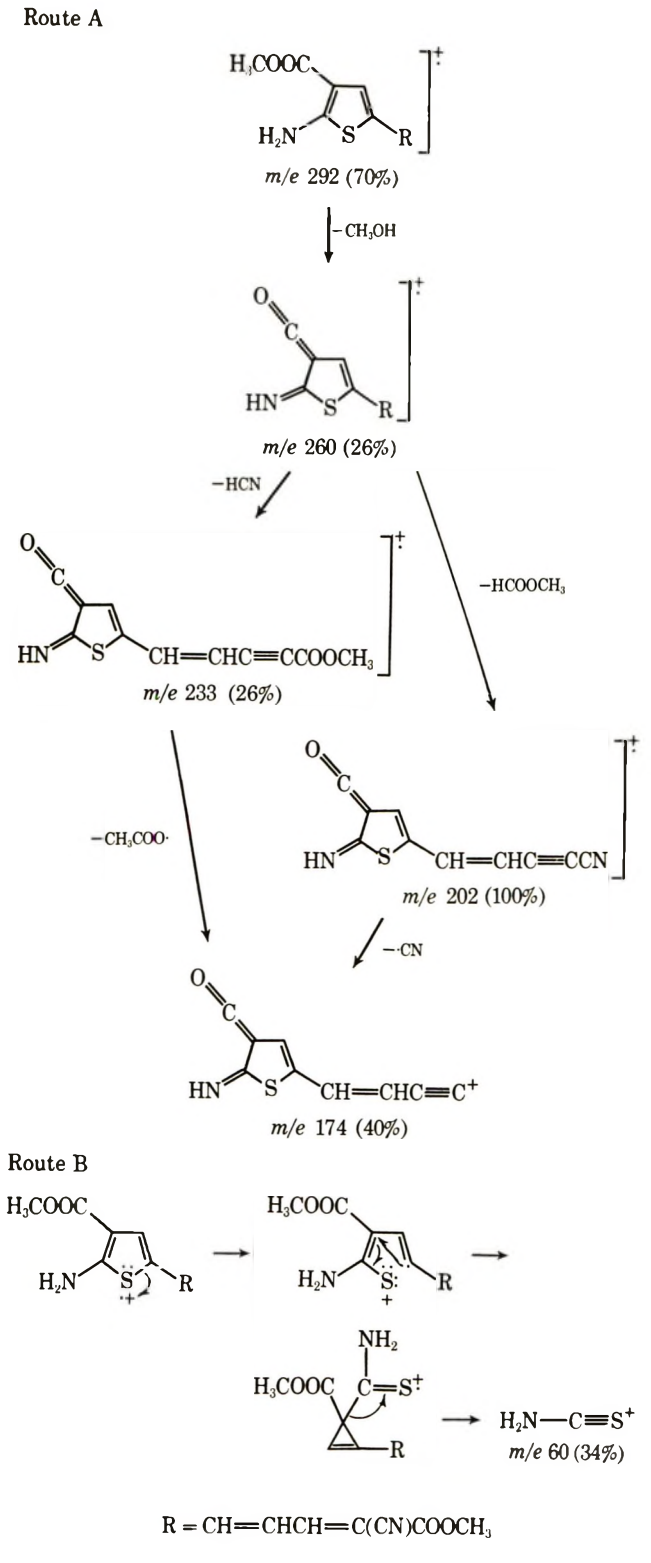


2

On the other hand, when methyl cyanoacetate (**4**) and thiophene-2-carboxaldehyde were mixed in morpholine or in piperidine directly, the same product **2** was also obtained in the range of 29–51% yields even when a 1:1 molar proportion of the reactants was used. The yields, in these reactions, were improved slightly by the use an excess of **4**, thus giving 32–71% **2**. It is impossible to isolate the expected cyanoacrylate **1** in any case. Furthermore, aminals[3–5] are commonly produced by the reaction of a secondary amine with an aldehyde;

(1) Laboratory of Chemistry, Utsunomiya University, Utsunomiya, Japan.
(2) H. Yasuda, T. Hayashi, and H. Midorikawa, *J. Org. Chem.*, **35**, 1234 (1970).
(3) C. Mannich and H. Davidsen, *Chem. Ber.*, **69**, 2106 (1936).
(4) A. Dornow and W. Schacht, *ibid.*, **82**, 464 (1949).
(5) R. Dulou, E. Elkik, and A. Veillard, *Bull. Soc. Chim. Fr.*, 967 (1960).

SCHEME I



however, 1,1-di(*N*-morpholine)- or 1,1-di(*N*-piperidino)-thienylmethanes could not be isolated in each reaction.

Elemental analysis and a mass spectral determination establish the molecular formula of **2** as $C_{13}H_{12}O_4N_2S$. Hydrogenation of **2** over palladium/carbon led to colorless oily mixtures of nondistillable materials. The ir and nmr spectra of **2** (see Experimental Section) provide support for the required structural feature. In the nmr spectrum a rather large coupling constant between two olefinic protons suggests the *trans* configuration about C=C bond. The structure of **2** is amply supported by mass spectral data. Based upon recent studies of the mass spectral fragmentation of thiophenes,[6] routes A and B have suggested for the observed fragmentation of **2** (Scheme I). A number of the postulated transformations received support from the metastable ions. Elimination of methanol appears to be the primary mode (route A) of molecular ion (*m/e* 292) fragmentation. Formation of the *m/e* 260 ion is a transformation characteristic anthranilic acid.[7] Loss of HCN or $HCOOCH_3$ from the *m/e* 260 ion could then lead to the ions at *m/e* 233 and 202. The *m/e* 174 ion might then arise from the *m/e* 233 ion by loss of $CH_3COO\cdot$, and from the *m/e* 202 ion by loss of $\cdot CN$. Pertinent aspects of the remaining mass spectrum can be interpreted by formation of the *m/e* 60 ion from the molecular ion as suggested by route B.

The formation of **2** from the cyanoacrylate **1** with morpholine or piperidine is of mechanistic interest. We proposed that the overall reaction may be rationalize by the sequence outlined in Scheme II. It is plausible that the initial attack of the base will occur both at the β carbon atom of the α,β unsaturation and the 5 position of thiophene ring in **1**. Thus, the addition of the base to the β carbon results in the formation of the amino ester intermediate **3**. This amino ester formation resembles the attack of secondary amines on the 1,2 or 2,3 double bond of 1-cyanoallenes, giving the corresponding enamines.[8] Similar addition has also been observed in the reaction of norbornanones with morpholine.[9] In general, cleavage of substituted tertiary amines gives the iminium cation and the anion structure as the results of α elimination.[10-15] It therefore appears that the formation of **4** and quaternary iminium hydroxide intermediate **5** can be visualized as proceeding through cleavage of the ester **3** by water molecule, which contains in the basic medium. When nucleophilic attack by the base appears to have occurred at the 5 position, the reaction would give the enamine intermediate **6**. This, then would cyclize between the SH and C≡N groups to afford the enamine **7**, which readily hydrolyzes to the β-thienylacrolein derivative **8**. The resulting product **8** could condense with **4** to give the required product **2**. This mechanism is closely similar to that previously reported.[2] Unfortunately, intermediates **5** and **8** could not be detected in the present investigation.

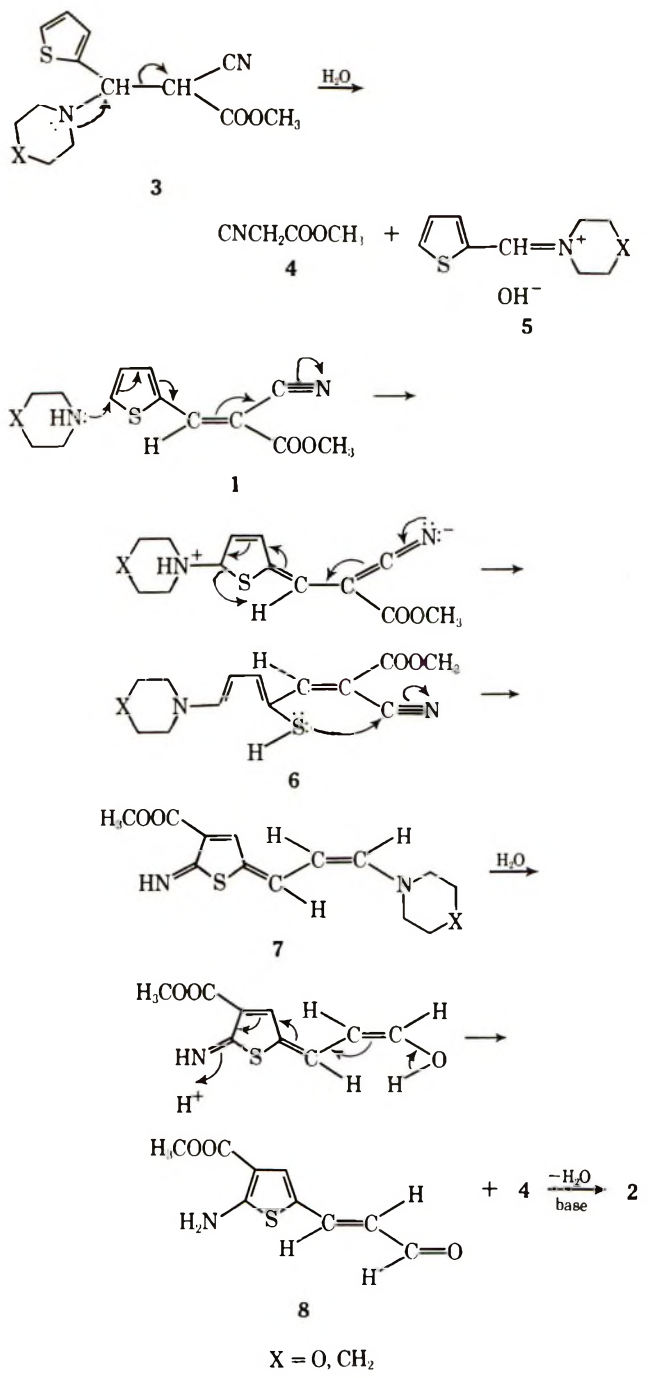
Experimental Section

Nmr spectra were recorded on a JNM-C-60 HL high-resolution nmr spectrometer in DMSO-d_6 with TMS as an internal standard. Ir spectra were determined in the KBr disks using a Perkin-Elmer 521 spectrophotometer. Mass spectra were obtained on a JNM-O1S spectrometer operating at 75 eV. Uv spectra were measured with a Cary Model 14 spectrometer.

Methyl α-Cyano-β-(2-thienyl)acrylate (1).—To a mixture of thiophene-2-carboxaldehyde (6.0 g, 0.054 mol) and methyl cyano-

(6) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967.
(7) K. Biemann, *Angew. Chem.*, **74**, 102 (1962).
(8) P. M. Greaves and S. R. Landor, *Chem. Commun.*, 322 (1966).
(9) R. D. Bach, *J. Org. Chem.*, **33**, 1647 (1968).
(10) A. R. Katritzky, *J. Chem. Soc.*, 2586 (1955).
(11) H. Böhme and D. Morf, *Chem. Ber.*, **91**, 660 (1958).
(12) R. E. Lyle, P. S. Anderson, C. K. Spicer, S. S. Pelosi, and D. A. Nelson, *Angew. Chem.*, **75**, 386 (1963).
(13) P. S. Anderson and P. E. Lyle, *Tetrahedron Lett.*, 163 (1964).
(14) N. J. Bauld and Y. S. Rim, *J. Amer. Chem. Soc.*, **89**, 6763 (1967).
(15) H. J. Dauben, Jr., and D. F. Rhodes, *ibid.*, **89**, 6764 (1967).

SCHEME II



acetate (6.4 g, 0.065 mol) was added piperidine (0.1 ml), and the mixture was allowed to stand for 4 hr at room temperature. The solid that separated was collected on a filter, washed with diluted methanol, and dried. One recrystallization from methanol gave 8.4 g (96%) of **1** as faintly yellow needles, mp 111–112°.

Anal. Calcd for $C_9H_7O_2NS$: C, 55.96; H, 3.63; N, 8.25. Found: C, 56.39; H, 3.61; N, 8.04.

Reaction of 1 with Piperidine.—A mixture of **1** (5.0 g, 0.026 mol) and 30 ml of piperidine containing 1 drop of water was mechanically stirred at room temperature for 40 min. The solution immediately turned a dark reddish brown color and an exothermic reaction took place. Dark brown solid began to precipitate after 15 min. After the mixture was allowed to stand overnight, the colored crystalline product that separated was collected on a filter, washed with methanol, and recrystallized from pyridine–ethanol to give 1.8 g (48%) of **2** as reddish brown short needles, mp 262–263°. The combined filtrate and washes were diluted with water, and the resulting colored solid recrystallized from the same solvent to yield 0.8 g [total 2.6 g (69%)] of pure **2** (the mother liquor in the above recrystallizations must be dry; the expected product **5** or **8** is almost impossible to separate): uv max ($CHCl_3$) 274 mμ (ε 15,000), 313 (8400), 458 (49,000); ir (KBr disk) 3358, 3258 (NH_2), 2214 (α,β-unsaturated C≡N), 1712 (α,β-unsaturated ester C=O), 1688 (α,β-unsaturated ester C=O, directly attached to thiophene ring), 1522, 1438, 1355, and 852 cm^{-1} (thiophene ring); nmr (DMSO-d_6) δ 3.70, 3.73 ($2COOCH_3$), 6.38 (q, H_β, $J_{\alpha\beta}$ = 11.2 Hz, $J_{\beta\gamma}$ = 14.5 Hz, $J_{\alpha\gamma}$ = ~0Hz), 7.62 (d, H_γ, $J_{\beta\gamma}$ = 14.5 Hz), 7.87 (d, H_α, $J_{\alpha\beta}$ = 11.2 Hz), 7.33 (s, thiophene ring H), and 8.24 (b, NH_2).

Anal. Calcd for $C_{13}H_{12}O_4N_2S$: C, 53.42; H, 4.10; N, 9.58; S, 10.95. Found: C, 53.42; H, 4.13; N, 9.53; S, 10.86.

Reaction of 1 with Morpholine.—A mixture of **1** (5.0 g, 0.026 mol) in 30 ml of morpholine containing 1 drop of water was mechanically stirred at room temperature for 40 min. The solution immediately became orange, and a dark brown solid precipitated. The precipitate on standing overnight was collected on a filter, washed with methanol, and recrystallized from pyridine–ethanol to form 2.1 g (56%) of the desired product **2**. Evaporation of the combined filtrate and washes gave dark brown tarry matter which could not be purified further.

Reaction of Thiophene-2-carboxaldehyde with Methyl Cyanoacetate (4) in Piperidine. Method A (1:1 Aldehyde–Ester).—To a stirred solution of **4** (1.1 g, 0.011 mol) in piperidine (5 ml) was added dropwise the aldehyde (1.2 g, 0.011 mol) at room temperature, and the stirring was continued for 20 min. The solution became reddish brown and an exothermic reaction took place. The mixture on standing overnight was diluted with methanol (15 ml), and the resulting colored solid recrystallized from pyridine–ethanol to give 0.8 g (51%) of the required product **2**. Purification of colored residual oil, followed by evaporation of the basic solvent at diminished pressure, gave no cyano ester **1** or other by-products.

Method B (1:2 Aldehyde–Ester).—In a procedure much like that of **A**, the aldehyde (1.2 g, 0.011 mol) and **4** (2.2 g, 0.022 mol) in piperidine (5 ml) were stirred for 20 min at room temperature. After the mixture was allowed to stand overnight, it was diluted with methanol (15 ml). The colored solid that separated was collected and recrystallized from pyridine–ethanol to yield 1.1 g (71%) of **2**. Evaporation of mother liquor afforded a negligible amount of oily matter which could not be purified further.

Reaction of Thiophene-2-carboxaldehyde with 4 in Morpholine. Method C (1:1 Aldehyde–Ester).—The aldehyde (1.2 g, 0.011 mol) was placed in 1.1 g (0.011 mol) of **4** in morpholine (5 ml) at room temperature. The mixture was stirred for 20 min and then allowed to stand overnight. The mixture became reddish brown, and dark brown solid precipitated. The reaction mixture on dilution with methanol (15 ml) was filtered to remove the crude **2**. One recrystallization from pyridine–ethanol gave 0.45 g (29%) of pure **2**. The residues on removal of the combined filtrate and washes and of mother liquor were not investigated further.

Method D (1:2 Aldehyde–Ester).—In essentially the procedure of *C*, a mixture of **4** (2.2 g, 0.022 mol) and the aldehyde (1.2 g, 0.011 mol) in morpholine (5 ml) was mechanically stirred for 20 min at room temperature. The reaction mixture on standing overnight was filtered and the residue was washed with methanol. After recrystallization from pyridine–ethanol a 32% yield (0.5 g) of **2** was obtained. The combined filtrate and washes were concentrated *in vacuo* to a dark brown oil, and no purification was attempted.

Attempted Catalytic Hydrogenation of 2.—A mixture of **2** (2.0 g, 0.010 mol) and 5% palladium/carbon catalyst (0.20 g) in ethanol (100 ml) was treated with hydrogen gas. The solution was changed to a colorless one and 0.042 mol of the gas was absorbed. Removal of solvent and the catalyst gave an almost colorless oil which could not be purified by fractional distillation under diminished pressure.

Registry No.—**1**, 29577-54-6; **2**, 29577-55-7.

Acknowledgment.—The authors express their deep gratitude to Professor Dr. Taro Hayashi, Professor Dr. Tatsuo Takeshima, and Professor Dr. Yoshihisa Kaneko for continuous encouragement. Nmr analyses were performed by Dr. Toshio Hayashi. We are also indebted to Dr. Haruo Homma and his staff for microchemical analyses.

Application of Europium(III) Chelate Induced Chemical Shifts to Stereochemical Assignments of Isomeric Perhydrophenalenols

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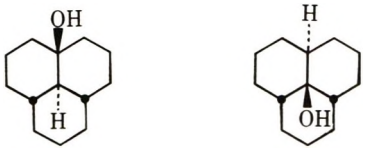
Use of paramagnetic chelates of europium(III) as described by Hinckley[1] and Sanders and Williams[2] to induce large chemical shifts in the nmr spectra of alcohols promises to be an extremely powerful tool for structure determination. In the most favorable instances complex spectra may be reduced to first-order spectra without appreciable loss of resolution thus enabling one to distinguish nonequivalence, multiplicities, and coupling constants directly from the spectrum. Described here is the use of this technique in resolving the signals due to the stereochemically significant protons of *trans,-trans, trans*-perhydro-3a-phenalenol (**1**)[3] and *cis,cis,-trans*-perhydro-9b-phenalenol (**2**).[4]



1 **2**

While there has been considerable recent interest[3-5] in the synthesis and reactions of perhydrophenalenols, assignment of structure and stereochemistry to the various isomers is often difficult owing to the fact that the nmr spectra are relatively uninformative in that they are characterized by broad envelopes between δ 0.5 and 2. Expedients which have been employed include observing whether the compounds exhibit "doublet-like" spectra of the *trans*-decalin type or the "singlet-like" spectra of the *cis*-decalin type. Conversion of the alcohol to a *p*-nitrobenzoate has also been used to induce small chemical shifts (*ca.* 1–2 ppm) in neighboring protons.

At 60 MHz the nmr spectrum of **1** (50 mg, 0.26 mmol) in 0.5 ml of $CDCl_3$ consists of a broad absorption for the carbon-bound protons between 0.5 and 2 ppm from internal TMS. Addition of 135 mg (0.19 mmol) of tris-(dipivalomethanato)europium(III) to the solution produces a spectrum in which the signals due to these protons are spread over a range of 7.5 ppm from δ 2.5 to 10. The most useful signals for assigning a structure are those shown in Figure 1.

Six of the 21 protons bound to carbon in **1** give rise to three sets of two-proton multiplets between δ 8 and 10. These signals are not well resolved and are assigned to the equatorial protons at C-3 and C-4, the axial protons at C-2 and C-5, and the axial protons at C-6a and

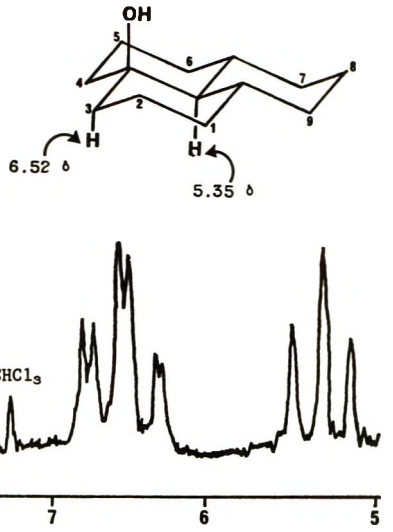


Figure 1.—Portion of the 60-MHz nmr spectrum of **1** in $CDCl_3$ in the presence of $Eu(DPM)_3$.

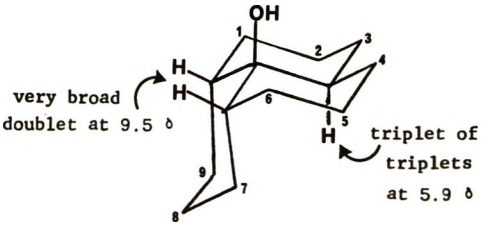
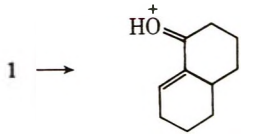


Figure 2.—Assignment of chemical shifts of stereochemically important protons of **2** from 60-MHz nmr spectrum in $CDCl_3$ in the presence of $Eu(DPM)_3$.

C-9a in accordance with the principle that the largest paramagnetic shifts should occur at the protons nearest the hydroxyl group.[6] The two-proton signal at δ 6.52 may be assigned as shown in Figure 1 to the axial protons at C-3 and C-4 which appear as a doublet of triplets because the proton at C-3 (or C-4) is coupled equally to the vicinal axial proton at C-2 (or C-5) and to the geminal equatorial proton at C-3 (or C-4) with a coupling constant of 13 Hz, as well as to the vicinal equatorial proton at C-2 (or C-5) with a coupling constant of 3 Hz. The sharp triplet in Figure 1 at δ 5.35 corresponds in area to one proton, and because of its multiplicity it must correspond to unique axial proton at C-9b. The splitting of 12 Hz requires a trans-diaxial orientation of this proton with two equivalent protons and further, since eight other protons in the molecule give signals at lower field in the presence of $Eu(DPM)_3$, it cannot be cis to the hydroxyl group. These observations and the mass spectral data depicted in eq 1 are consistent



(1)

m/e 151, base peak

only with structure **1** out of a total of the ten tertiary perhydrophenalenol isomers.

The type of cleavage shown in eq 1 can occur only

(1) C. C. Hinckley, *J. Amer. Chem. Soc.*, **91**, 5160 (1969); *J. Org. Chem.*, **35**, 2834 (1970).

(2) J. K. M. Sanders and D. H. Williams, *Chem. Commun.*, 422 (1970).

(3) H. C. Brown and E. Negishi, *J. Amer. Chem. Soc.*, **89**, 5478 (1967).

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(5) F. A. Carey and H. S. Tremper, *ibid.*, **36**, 758 (1971).

(6) P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J. Amer. Chem. Soc.*, **92**, 5734, 5737 (1970); G. H. Wahl, Jr., and M. R. Peterson, Jr., *Chem. Commun.*, 1167 (1970).

when the hydroxyl group is at C-3a, -6a, or -9a.[7] The base peak for 2 is at m/e 176 corresponding to loss of H_2O from the molecular ion.

The nmr spectrum of 2 (0.31 mmol) in 0.5 ml of $CDCl_3$ containing 0.21 mmol of $Eu(DPM)_3$ was completely consistent with the structure proposed by Brown.[3] Here, as in 1, considerable simplification of the spectrum results from the near equality of the geminal and trans-diaxial coupling constants. The lowest field signal (δ 9.5) is a very broad doublet assigned to the protons at C-6a and C-9a, consistent with the 1,2-cis relationship of these protons to the complexed hydroxyl and the expected large (13 Hz) coupling to the axial proton at C-7 (or C-9) with smaller gauche couplings to both protons at C-6 (or C-1) and the equatorial proton at C-7 (or C-9).

The signals from the axial protons at C-1 and C-6 appear as a broadened triplet at δ 8.6, and the signals from the axial protons at C-3 and C-4 appear as a quartet of doublets at δ 7.4. The unique axial proton at C-3a gives rise to a triplet of triplets at δ 5.9 resulting from coupling to the two equivalent axial protons at C-3 and C-4 (J = 13 Hz) and to two equivalent equatorial protons at C-3 and C-4 (J = 3 Hz).

It seems reasonable that the stereochemistry of all perhydrophenalenols, as well as related systems, should be capable of being determined by use of $Eu(DPM)_3$ induced chemical shifts in conjunction with mass spectrometry.

Experimental Section

Nmr spectra were determined on a Hitachi Perkin-Elmer R-20 spectrometer at 30°. Mass spectra were measured on a Hitachi Perkin-Elmer RMU-6E instrument using an ionizing potential of 70 eV and an unheated inlet.

Compound 1 was prepared as described previously,[5] while 2 was provided by W. C. Dickason and H. C. Brown of Purdue University.

Registry No.—1, 27390-92-7; 2, 16664-34-9.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. Thanks are also given to Professor Donald Hunt for a gift of $Eu(DPM)_3$ and to Professor H. C. Brown and Dr. W. C. Dickason for a sample of 2 and numerous helpful comments.

(7) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, p 107.

Differences in Stability, Gas–Liquid Chromatographic Retention Times, and Esterification Rates for the Diastereoisomers of 2,3-Dimethylsuccinic Acid and Its Esters

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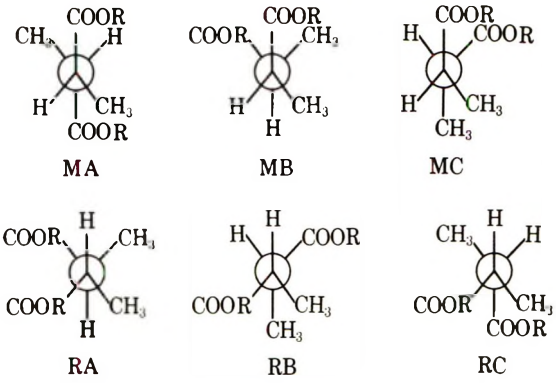
This report is concerned with the differences that are observed in certain properties of diastereoisomers of 2,3-dimethylsuccinic acid, and its esters, which arise from conformational factors. Equilibrium studies of the acid diastereoisomers have been previously reported;[1] however, the analysis of the diastereoisomers by gas–liquid chromatography, as used in this study, should be superior to the previously used analytical method of mixture melting points.

It has been pointed out[2] that, if only steric interactions are considered to be present in the diastereoisomers of 2,3-dimethylsuccinic acid, conformer MA would be predicted to be the most stable configuration. That the equilibrium of such a system is not influenced by entropy differences of the meso and racemic forms (they are essentially equivalent entropywise) has been noted.[3]



It has been reported[4] that the meso isomer, as predicted, was experimentally determined to be more stable than the racemate and this result has been generally cited[2,5] as an example of diastereoisomer equilibrium. However, Eberson[1] more recently found that the racemate was somewhat more stable and explained this by assuming a stabilizing effect due to intermolecular hydrogen bonding in the racemate conformer RC. Cason and Schmitz[6] postulated cyclic hydrogen-bonded structures for both the meso and racemic forms to explain somewhat similar reported stabilities. The present study finds the racemate–meso ratio of acids at equilibrium in 5 N hydrochloric acid to be about 2:1 (Table I) which would favor Eberson's conclusion. The finding of Paolillo and Temussi,[7] using nmr, that the racemate in water consists mainly of the RA conformer rather than the RC one does not affect Eberson's general conclusions.

TABLE I
RESULTS OF THE EQUILIBRIUM EXPERIMENTS

Equilibrium mixture	% of the diastereoisomers— Meso	Racemate
Acids	32.4	67.6
Methyl esters	49.5	50.5
Isopropyl esters	74.4	25.6

Since the increased stability of the acid racemate can be attributed to formation of intramolecular hydrogen bonds, which are not formed in the diesters, it was rea-

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(3) L. I. Peterson, *J. Amer. Chem. Soc.*, **89**, 2677 (1967).
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(5) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 139.
(6) J. Cason and F. J. Schmitz, *J. Org. Chem.*, **28**, 555 (1963).
(7) L. Paolillo and P. A. Temussi, *Ric. Sci.*, **37**, 687 (1967).

soned that the "steric interaction" argument might hold true for the diesters in producing a more stable meso form. The results of the equilibrium experiments with methyl and isopropyl esters of 2,3-dimethylsuccinic acid are given in Table I. The methyl esters of the meso and racemic diastereoisomers are present in almost equal amounts at equilibrium, whereas in the case of the isopropyl esters, the meso is definitely the more stable form. Presumably the steric interaction of the more bulky isopropyl groups outweighs any interaction of the polar portions of the molecule.

In the glc analysis of the diastereoisomer esters, the racemic methyl and isopropyl esters were found to have greater retention times than those of the corresponding meso ones (Table II). This was expected[8] as was the observation that the presumably hydrogen-bonded racemic acid had a retention time less than that of the meso form. The direction of the change in the relative retention time of the methyl (1.18), isopropyl (1.05), and trimethylsilyl (1.00) esters can be explained by the increased shielding of the polar groups in going to the more bulky ester groups.

TABLE II
RELATIVE RETENTION TIMES OF THE DIASTEREOISOMERS OF 2,3-DIMETHYLSUCCINIC ACID AND ITS ESTERS[a]

Diastereoisomers	Relative retention time, racemate/meso
Acids	0.76
Methyl esters	1.18
Isopropyl esters	1.05
Trimethylsilyl esters	1.00

[a] All esters were chromatographed under the same conditions.

The ratios of the two diastereoisomeric dimethyl esters present in partly esterified mixtures, shown in Table III, indicate that the racemic acid esterifies faster than the meso. Unimolecular rate constants for the two acid forms were compared as if the two acid groups esterify independently. From these calculations, discussed in the Experimental Section, a rate constant 30% greater for the racemic acid is indicated. An actual determination of the esterification rates k_1 and k_2 for each acid form would be necessary in order to interpret the esterification rate differences.

TABLE III
RESULTS OF THE ESTERIFICATION EXPERIMENTS

% acid groups reacted (a)	% of the methyl ester diastereoisomers: Meso (m)	Racemate (r)	$k_{racemate}/k_{meso}$
32	30.2	69.8	1.30
74	30.9	69.1	1.33
90	34.7	65.3	1.23
(100)	37.2	62.8	

Experimental Section

Materials.—By means of melting point and gas–liquid chromatography, 2,3-dimethylsuccinic acid (K and K Laboratories, Plainview, N. Y.) was found to consist of 99.8% of the meso form. Mixtures of the meso and racemic acid forms from which esters were prepared were obtained by heating the meso form with 5 *N* hydrochloric acid. The trimethylsilyl esters were prepared with the silylation reagent Tri-Sil (Pierce Chemical Co., Rockford, Ill.).

Gas–Liquid Chromatography.—For chromatography of the esters, a 20 ft × 1/8 in. column packed with 3% XE-60 on 80–100 mesh Chromosorb W was used. The column temperature was 200° and the helium flow was 30 ml/min. Even when chromatographed separately (a sample of the racemic acid was obtained from the equilibrium mixture of the acids by means of crystallization from concentrated hydrochloric acid), the retention times of the two trimethylsilyl esters showed no difference. The acid diastereoisomers were chromatographed on a column 6 ft × 1/8 in. packed with 20% diethylene glycol adipate and 3% phosphoric acid on 60–80 mesh Gas-Chrom P. Peak shapes for the acids were distorted so that this method would not be suitable for analytical purposes.

Equilibrium Experiments.—Samples of the meso acid, approximately 0.2 g in 10 ml of 5 *N* hydrochloric acid, were sealed in glass tubes and kept at 125°. Analysis of the samples by glc of the methyl esters showed that equilibrium had been reached within 100 hr. Methyl and isopropyl esters prepared from the meso acid, approximately 0.2-g samples in 10 ml of the corresponding alcohol containing 0.1 *N* sodium alcoholate, reached equilibrium within 50 hr. Analyses of the diastereoisomers are based on peak-area measurements. Results are given in Table II.

Relative Esterfication Rates.—A sample of the meso acid heated to 125° in 5 *N* hydrochloric acid for 80 hr provided a mixture of 37.2% meso and 62.8% racemic acids. Samples of this acid mixture (0.2 g) were partly esterified by refluxing in 25 ml of methanol containing 0.1 g of concentrated sulfuric acid for approximately 12, 30, and 60 min. The per cent of carboxylic acid groups reacted was determined by titration and the ratio of the two diesters formed was analyzed by glc. Relative esterification rates of the two acids were calculated on the assumption that the acid groups react independently, by use of the equation

$$\frac{k_{racemate}}{k_{meso}} = \frac{\log [1 - (\text{fraction of racemate diester formed})^{1/2}]}{\log [1 - (\text{fraction of meso diester formed})^{1/2}]} = \frac{\log [1 - (a/100)(r/62.8)^{1/2}]}{\log [1 - (a/100)(m/37.2)^{1/2}]}$$

where a is the per cent of the acid groups reacted, and m and r are the per cent areas of the chromatogram for the meso and racemate diesters. The results are shown in Table III.

Registry No.—*meso*-2,3-Dimethylsuccinic acid, 608-40-2; *rac*-2,3-dimethylsuccinic acid, 608-39-9; meso methyl ester, 29800-12-2; racemic methyl ester, 29913-52-8; meso isopropyl ester, 29800-13-3; racemic isopropyl ester, 29800-14-4; meso trimethylsilyl ester, 29800-15-5; racemic trimethylsilyl ester, 29800-16-6.

(8) D. Nurok, G. L. Taylor, and A. M. Stephen, *J. Chem. Soc. B*, 291 (1968).

^{13}C–H Coupling Constants as a Probe of Ortho-Substituent Effects

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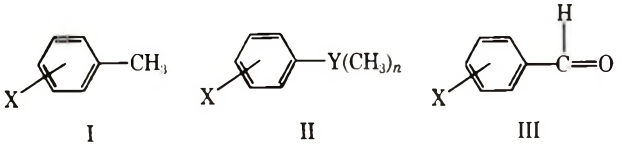
Although attempts at semiquantitative correlations of structure with reactivity in substituted aromatics have been made, ortho substituents are usually not included in linear free energy relationships. It has generally been assumed that steric factors as well as electronic ones would be an important consideration in

such systems. However, recent work has indicated that, in fact, steric factors should not have an effect in many of these ortho-substituted systems, but that no one universal set of σ_o constants could be derived.[1]

Recently we have shown the existence of linear correlations between σ_m and σ_p and the magnitude of the ^{13}C–H coupling constants in compounds of types I, II, and III, where Y = C (n = 3), N (n = 2), and O (n = 1).[2]



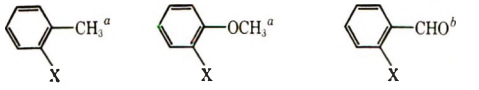
I II III

Since ^{13}C–H coupling constants are independent of anisotropy effects and are generally believed to be a function of the effective nuclear charge of carbon and the s character in the C–H bond,[3] this parameter should be an excellent probe into the electronic nature of the ground state of ortho-substituted aromatics. We have, therefore, measured the ^{13}C–H coupling constants of ortho-substituted toluenes, anisoles, and benzaldehydes. These three series were chosen because of the relatively large values of the J–σ slopes of the meta and para analogs and also because these systems contain C–H sites on electron-releasing (toluenes and anisoles) and electron-withdrawing (benzaldehydes) groups.

Methyl ^{13}C–H coupling constants and ortho σ constants are presented in Table I. The ortho σ constants

TABLE I

^{13}C–H COUPLING CONSTANTS (±0.2 Hz) AND σ_o CONSTANTS



X	J	σ	J	σ	J	σ
NO_2	129.4	2.0	145.4	1.7	192.1	2.26
CHO	127.8	1.1	144.6	1.2	183.0	1.10
CO_2H	128.0	1.2				
CN	127.9	1.2				
F	127.9	1.2	144.1	0.8	182.5	1.04
Cl	127.9	1.2	144.1	0.8	182.8	1.08
Br	127.8	1.1	144.3	0.9	183.4	1.15
I	128.2	1.3	144.2	0.9		
OH	126.9	0.6			177.7	0.43
OCH_3	126.9	0.6	143.3	0.2	180.3	0.76
H	125.8	−0.06	143.0	0.0	174.9	0.076
CH_3	125.7	−0.12	143.0	0.0	173.8	−0.063
C_2H_5	125.6	−0.17				
NH_2	125.6	−0.17	143.3	0.2	171.8	−0.32
$N(CH_3)_2$	126.4	0.3				

[a] 0.30 g or ml of solute per 1.0 ml of CCl_4. [b] 0.80 g or ml of solute per 1.0 ml of $CHCl_3$.

were obtained from the equation $J = \rho\sigma + C$, where J is the ortho coupling constant and ρ and C are the least-squares slope and intercept, respectively, for the J–σ plot of the appropriate meta- and para-substituted series. For the toluene series, ρ = 1.72 and C = 125.9;[2a] for the anisole series the slope obtained by using σ^* values for the p-CHO, p-NO_2, and p-CN derivatives was chosen, ρ = 1.38 and C = 143.0;[2a] for the benzaldehyde series ρ = 7.89 and C = 174.3.[2b,4] σ_o constants derived from the toluene and anisole series are believed to have uncertainties of *ca.* ±0.1–0.2; those from the benzaldehyde, ± <0.05.

An examination of the data presented in Table I leads to several interesting observations.

(1) The σ_o constants for a particular substituent are roughly similar in all three series of compounds, but it is also obvious that σ_o for a given substituent in some cases is sensitive to the nature of the remainder of the molecule. Thus because of the relatively large uncertainties in the toluene and anisole ortho σ constants, σ_o for fluorine is the same for all three series within experimental error; on the other hand, the difference between σ_o for the nitro group obtained from the anisole derivative relative to the value obtained from the benzaldehyde derivative is outside experimental error.

(2) The σ_o constants are generally considerably greater in magnitude than the related σ_m and σ_p constants. This appears to be true primarily for electron-attracting substituents and is probably due to the greater inductive (field) effect in the ortho position.

(3) The quite positive σ_o values for the OH and OCH_3 groups indicate the predominance of the electron-withdrawing inductive effect over the electron-releasing resonance effect.

(4) The fact that the σ constants for the o-NH_2 group derived from the benzaldehydes and toluenes are negative argues for the predominance of the resonance effect over the inductive effect. The difference in electronic function between the OH(OCH_3) and NH_2 groups can be rationalized on the basis of oxygen's greater electronegativity. The positive σ_o constant derived from the anisole series can probably be attributed to intramolecular hydrogen bonding.

(5) The positive σ_o constant for the dimethylamino group can be ascribed to steric inhibition of resonance. Steric interaction of the ring methyl and N-methyl groups reduces electron release by resonance and thus produces a higher coupling constant and σ constant. This effect (in coupling constants) has been previously discussed.[5]

(6) The σ_o values for F and Cl are nearly identical in each of the three series. Since the $\sigma_{p\text{-F}}$ (+0.062) is considerably smaller than $\sigma_{p\text{-Cl}}$ (+0.277), the much greater inductive effect of F in the ortho position must be relatively more important than the +R resonance effect.

Experimental Section

Compounds studied were all commercial samples. Spectroquality CCl_4 and $CHCl_3$ (C_2H_5OH removed with alumina) were used as solvents. Coupling constants were obtained on a Varian A-60D nmr spectrometer using standard side-banding techniques.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to Research Corporation (Frederick Gardner Cottrell Grant) for support of this research.

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(2) (a) C. H. Yoder, R. H. Tuck, and R. E. Hess, *ibid.*, **91**, 539 (1969); (b) C. H. Yoder, C. D. Schaeffer, Jr., and R. E. Hess, unpublished results.

(3) D. M. Grant and W. M. Litchman, *J. Amer. Chem. Soc.*, **87**, 3994 (1965).

(4) For the least-squares analysis of 13 compounds ($CHCl_3$), standard deviation of residuals was found to be 0.416, correlation coefficient 0.993.

(5) C. H. Yoder, B. A. Kaduk, and R. E. Hess, *Tetrahedron Lett.*, 3711 (1970).

Synthesis and Hydrolysis of Hindered 2,2-Disubstituted 5-Cyanocyclopentanoneimines[1a]

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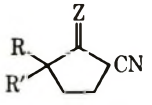
Previous attempts to hydrolyze 2,2-diphenyl-5-cyanocyclopentanoneimine (Ia, 2-amino-1-cyano-3,3-diphenylcyclopentene) to 2,2-diphenyl-5-cyanocyclopentanone (Ib) were unsuccessful.[2,3] The products isolated were the corresponding iminoamide, ketoamide, or decarboxylated ketone. Thus, the normally observed preferential hydrolysis of ketimine before nitrile was reversed in this case. The steric hindrance of the gem phenyl groups adjacent to the carbimino function was suggested to explain this anomaly since the desired selectivity was found in the dimethyl, diethyl, and ethylphenyl compounds.[3] Others have ascribed the decrease in reactivity of substituted ketimines toward hydrolysis to be related to increasing bulk of the groups attached to the carbon of the >C=NH.[4] We recently hydrolyzed the next higher homolog of Ia to 2,2-diphenyl-6-cyanocyclohexanone by using dioxane as the major solvent.[5] Since the 2,2-diphenyl groups did not prevent hydrolysis in the six-membered ring, the five-membered-ring case and related compounds were examined.

The synthesis and acid hydrolysis of these compounds were studied to determine the applicability of Newman's "six number." This concept has been



a, Z = NH
b, Z = O

Compd no.	R	R′
I	Ph	Ph
II	*i*-C_3H_7	Ph
III	*i*-C_3H_7	*i*-C_3H_7
IV	*c*-C_6H_{11}	Ph

effective in rationalizing data for addition–elimination reactions such as the ketimine hydrolyses considered here. The six numbers for Ia, IIa, IIIa, and IVa are 4, 8, 12, and 6, respectively.[6] The equality of phenyl and isopropyl groups for shielding effects is well known[7] as well as their opposite electronic effects. However, phenyl does not exert a constant steric effect[8] and there may occasionally be compensation by some polar effect. If the steric effect is controlling, the conversion of all but IIIa to the corresponding keto nitriles would be anticipated in reasonable yields.

Compounds Ia, IIa, IIIa, and IVa were synthesized by our previously developed route.[3] Acid hydrolysis of these iminonitriles (existing mainly as 1-amino-2-cyanocyclopentene tautomers[3,5,9]) proceeded in the order of difficulty predicted. Whereas type a compounds with R and R′ = hydrogens, dimethyls, diethyls, and ethylphenyl were hydrolyzed readily to their keto nitriles,[3] similar conditions were ineffective with the compounds reported here. However, changing the major solvent to dioxane and refluxing for several hours was quite satisfactory for the diphenyl Ia and cyclohexylphenyl IVa compounds which have six numbers of 4 and 6, respectively. A prolonged reaction time, 5 or 6 days, in refluxing dioxane gave some diisopropyl keto nitrile IIIb and a 62% yield of the isopropylphenyl keto nitrile IIb, six numbers of 12 and 8, respectively. The reexamination of the diphenyl and related compounds initiated by consideration of the "six number" again confirms the generalization that really large steric effects are observed only in compounds containing nine or more atoms in the 6 position.[6]

Experimental Section[10]

Disubstituted Acetonitriles.—The diphenyl compound was available.[3] The diisopropyl compound was obtained by extending the alkylation reaction reflux time to 18 hr for the preparation of ethyl diisopropylcyanoacetate,[11] saponification[12] for 44 hr followed by acidification to pH 2, and decarboxylation[12] in 57% overall yield. The phenylisopropyl compound was prepared by adding dropwise over 2 hr a solution of 146.4 g (1.25 mol) of phenylacetonitrile and 162 g (1.31 mol) of isopropyl bromide in 200 ml of anhydrous ether to 1.25 mol of lithium diethylamide[11] at a rate which allowed control of the exothermicity. The mixture was refluxed for 16 hr and worked up to give 167.5 g (84%) of isopropylphenylacetonitrile, bp 124–134° (15 mm) [lit.[13] 128–130° (15 mm)]. The cyclohexylphenyl compound was obtained by modifications of reported procedures.[13] To a solution of 32.6 g (0.2 mol) of bromocyclohexane in 200 ml of dimethyl sulfoxide was added simultaneously and separately 40 ml of 50% aqueous sodium hydroxide and 23.4 g (0.2 mol) of phenylacetonitrile at a rate that maintained the exothermic reaction between 45 and 50°. After the additions, stirring at 45° was continued for 3 hr. The cooled mixture was then diluted with water and extracted with three 100-ml portions of benzene and then two 100-ml portions of ether The Taranko work-up[13c] gave 25.6 g (64%) of product after vacuum distillation and solidification, mp 54–56.5° from hexane (lit.[14] 56–58°).

5-Chloro-2,2-disubstituted Pentanenitriles.—Adaptation of a published procedure for homologous compounds[3] gave the 2,2-diisopropyl compound, bp 131–140° (9 mm) (64%), the 2-isopropyl-2-phenyl compound, bp 167–173° (6 mm) (43%), and the 2-phenyl-2-cyclohexyl compound, bp 163–168° (0.8 mm) (52%) [lit.[14] 163° (0.7 mm)].

2,2-Disubstituted Hexanedinitriles.—The sodium cyanide–dimethyl sulfoxide method[15] gave the 2,2-diisopropyl compound,

(1) (a) Supported in part by an NSF Undergraduate Research Participation Grant, summer 1965. (b) Taken in part from the Senior Honors Theses of J. M. (1966), P. J. M. (1966), and S. T. H. (1968).

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(4) For leading references, see (a) P. L. Pickard and G. W. Polly, *J. Amer. Chem. Soc.*, **76**, 5169 (1954); (b) C. J. Thomas and I. Moyer Hunsberger, *J. Org. Chem.*, **33**, 2852 (1968); (c) F. A. Vingiello and A. Borkovec, *J. Amer. Chem. Soc.*, **77**, 3413 (1955).

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bp 176–178° (9 mm) (82%), the 2-isopropyl-2-phenyl compound, mp 71–72° from methanol, bp 183–185° (3 mm) (72%), and the 2-cyclohexyl-2-phenyl compound, mp 74–75° (lit.[14] mp 71–72°).

2,2-Disubstituted 5-Cyanocyclopentanoneimines.—The sodium hydride–dioxane procedure[3] gave the following compounds.

IIIa had mp 121–122° from 85% methanol; distilled at 155–165° (5 mm) (~100% yield of crude); ir ($CHCl_3$) 3500, 3400 (NH), 2190 (CN), and 1610 cm^{-1} (C=C).

Anal. Calcd for $C_{12}H_{20}N_2$: C, 74.95; H, 10.48, N, 14.57. Found: C, 74.92; H, 10.49; N, 14.57.

IIa had mp 119–119.5° (75%) from ethanol–water; ir ($CHCl_3$) 3495, 3400 (NH), 2195 (CN), and 1595 cm^{-1} (C=C).

Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.60; H, 8.02; N, 12.38. Found: C, 79.78; H, 8.11; N, 12.35.

IVa had mp 110–112° (lit.[14] 106–107°) (74%) from methanol; ir ($CHCl_3$) 3480, 3380 (NH), 2190 (CN), and 1640 cm^{-1} (C=C).

2,2-Disubstituted 5-Cyanocyclopentanones.—Ib was obtained by the hydrochloric acid–dioxane procedure[5] previously used for the cyclohexanone homolog. The product had mp 105–106.5° from ethyl acetate and was identical (mixture melting point not depressed and infrared spectrum) with a sample[16] available from an alternate synthesis.

A similar hydrolysis mixture of 4.0 g of IIa was refluxed with stirring for 5 days. To the cooled mixture was added 50 ml of water and three extractions with 60-ml portions of ether were carried out. The combined ether extracts were washed six times with equal volumes of water and then five times with fresh 50-ml portions of 10% sodium hydroxide. The mixture was shaken vigorously for about 3–4 min each. The combined basic extracts were cooled in ice, acidified to pH 2 with 6 *N* HCl, and allowed to stand in ice. The filtered, air-dried product weighed 2.5 g (62%) and melted at 68–70°. The analytical sample after four recrystallizations from ethanol had mp 68–69°; ir ($CHCl_3$) 2250 (CN) and 1755 cm^{-1} (CO).

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.08; H, 7.62; N, 6.06.

Numerous other hydrolysis attempts for shorter time periods in dioxane or in other solvents (toluene, methanol, polyphosphoric acid, glacial acetic acid, sulfuric acid) were ineffective or considerably less efficient as determined by infrared spectra of crude reaction product mixtures by nitrile absorption peaks for conjugated CN (IIa tautomer) and nonconjugated CN (IIb).

Refluxing IVa in hydrochloric acid–dioxane for 5 hr gave 91% crude IVb which after sublimation and recrystallization from hexane melted at 115–116°; ir ($CHCl_3$) 2245 (CN) and 1745 cm^{-1} (CO).

Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.98; H, 7.96; N, 5.24.

The diisopropyl compound IIIb was obtained by the same procedure as IIb but the reaction time was 6 days. Final distillation of the mixture gave 30% 2,2-diisopropylcyclopentanone, bp 54° (1 mm), and 40% IIIb, bp 103° (1 mm), ir (neat) 2250 (CN) and 1750 cm^{-1} (CO).

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.42; H, 9.77; N, 7.04.

The final product, 2,2-diisopropylcyclopentanone, had an infrared peak (neat) at 1735 cm^{-1} and no absorptions for NH or CN.

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.32; H, 11.71.

Many other hydrolyses of IIIa were attempted by varying solvents, concentrations, and times but were less satisfactory than the above procedure.

2,2-Diisopropylcyclopentanoneimine-5-carboxamide.—Polyphosphoric acid treatment[17] of IIIa gave a 60% yield of iminoamide: mp 154.5–155.5° from benzene; ir 3500, 3400, and 1760 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}N_2O$: C, 68.53; H, 10.55; N, 13.31. Found: C, 68.55; H, 10.70; N, 13.32.

2,2-Diisopropylcyclopentanone-5-carboxamide.—To 32 ml of 80% sulfuric acid at 100° was added 1 g of IIIa with stirring. After 1 hr the mixture was cooled and poured over crushed ice. The tan solid was unstable in air, in light, and at room temperature. Repeated crystallization by partially evaporating an ether solution and storage of the compound under nitrogen at −10° gave a white solid, mp 109° dec. Its ir was comparable with that of 2-ethyl-2-phenyl-6-carbamoylcyclohexanone.[5]

Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.60; H, 10.00; N, 6.64. Found: C, 68.93; H, 9.67; N, 6.73, 6.69.

Registry No.—IIa, 29411-08-3; IIb, 29411-09-4; IIIa, 29411-10-7; IIIb, 29411-11-8; IVa, 5358-98-5; IVb, 29411-13-0; 2,2-diisopropylcyclopentanone, 29411-14-1; 2,2-diisopropylcyclopentanoneimine-5-carboxamide, 29411-15-2; 2,2-diisopropylcyclopentanone-5-carboxamide, 29411-16-3.

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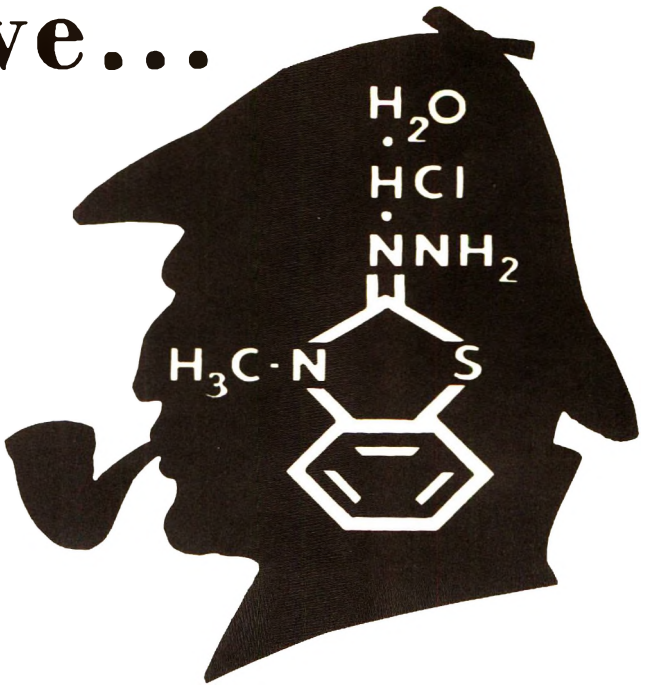

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